US010316066B2

(12) **United States Patent**
Tangy et al.

(10) **Patent No.: US 10,316,066 B2**
(45) **Date of Patent: Jun. 11, 2019**

(54) **DENGUE VIRUS CHIMERIC POLYEPITOPE COMPOSED OF FRAGMENTS OF NON-STRUCTURAL PROTEINS AND ITS USE IN AN IMMUNOGENIC COMPOSITION AGAINST DENGUE VIRUS INFECTION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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§ 371 (c)(1),
(2) Date: **Dec. 19, 2016**

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PCT Pub. Date: **Dec. 30, 2015**

(65) **Prior Publication Data**

US 2017/0158740 A1 Jun. 8, 2017

(30) **Foreign Application Priority Data**

Jun. 23, 2014 (EP) 14305984

(51) **Int. Cl.**
A61K 39/12 (2006.01)
C07K 14/005 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***C07K 14/005*** (2013.01); ***A61K 39/12*** (2013.01); ***C07K 14/1825*** (2013.01); ***C12N 7/00*** (2013.01);
(Continued)

(58) **Field of Classification Search**
None
See application file for complete search history.

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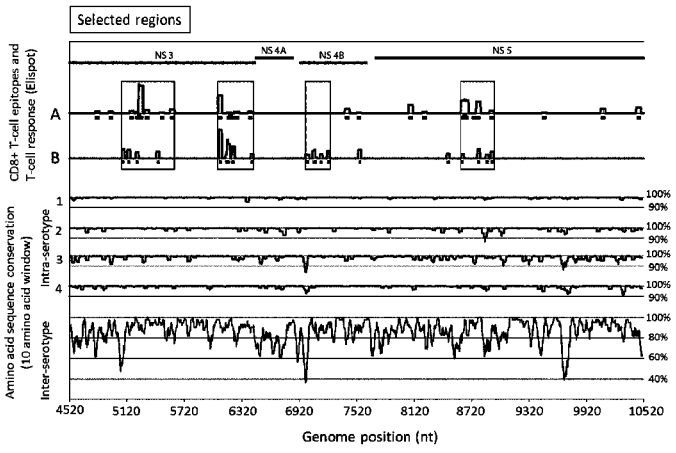
Primary Examiner — Janet L Andres
Assistant Examiner — Stuart W Snyder
(74) *Attorney, Agent, or Firm* — Arrigo, Lee, Guttman & Mouta-Bellum LLP

(57) **ABSTRACT**

The present invention is directed to a dengue virus chimeric polyepitope composed of fragments of non-structural proteins and its use in an immunogenic composition against dengue virus infection. The present invention provides means, in particular polynucleotides, vectors, cells and methods to produce vectors expressing said chimeric polyepitopes, in particular vectors consisting of recombinant measles virus (MV) particles. The present invention also relates to the use of the recombinant MV particles, in
(Continued)



particular under the form of a composition or of a vaccine, for the prevention and/or treatment of a dengue virus infection.

10 Claims, 27 Drawing Sheets

Specification includes a Sequence Listing.

(51) **Int. Cl.**

C07K 14/18	(2006.01)
C12N 7/00	(2006.01)
A61K 39/00	(2006.01)

(52) **U.S. Cl.**

CPC *A61K 2039/525* (2013.01); *A61K 2039/5254* (2013.01); *A61K 2039/54* (2013.01); *A61K 2039/70* (2013.01); *C07K 2319/00* (2013.01); *C12N 2760/18441* (2013.01); *C12N 2760/18443* (2013.01); *C12N 2770/24134* (2013.01); *Y02A 50/386* (2018.01)

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WO	2011/163628 A2	12/2011		
WO	WO 2011/163628 A2 *	12/2011	.....	A61K 39/12
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WO	WO 2012/178196 A2 *	12/2012	.....	A61K 39/12

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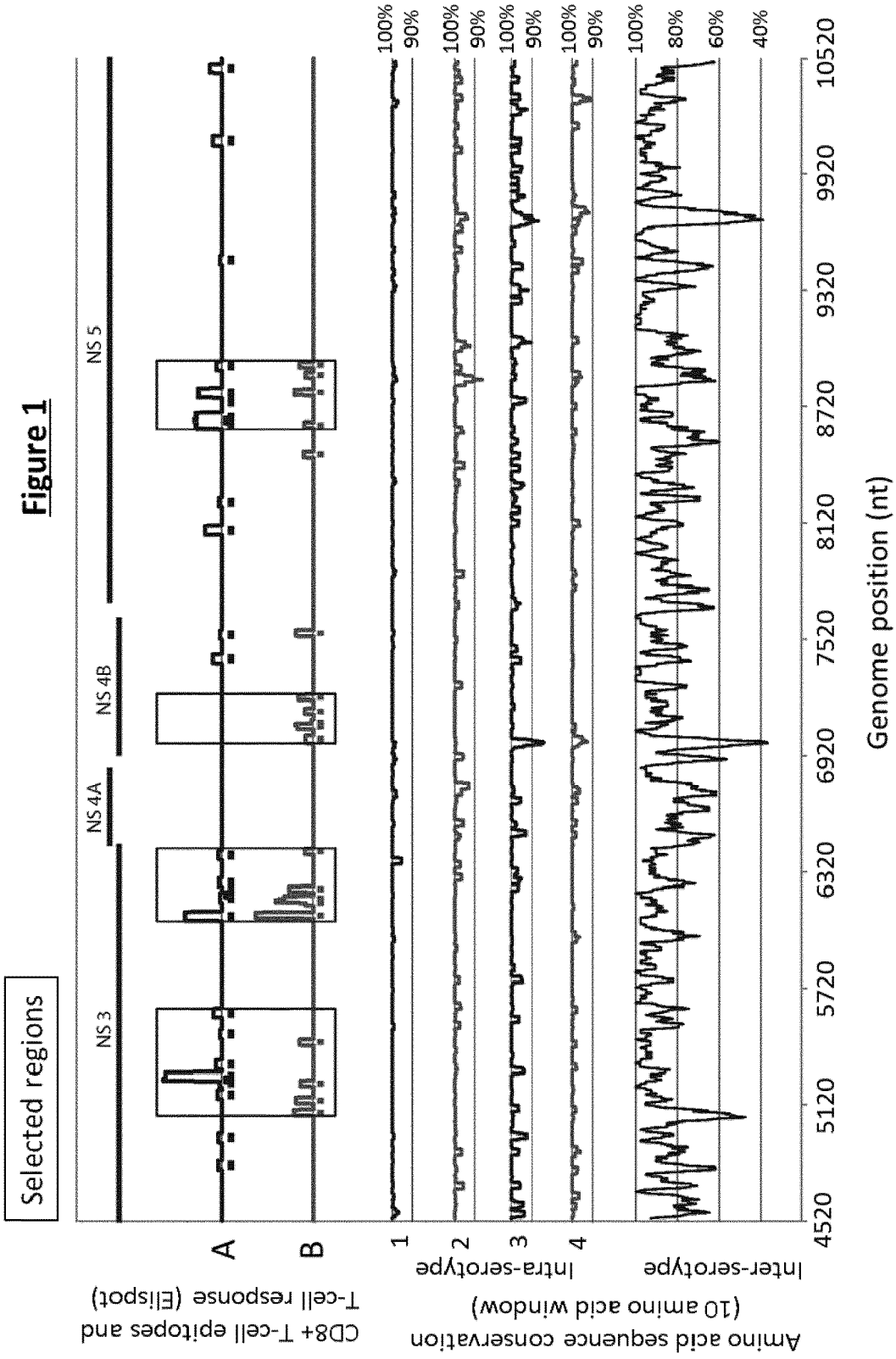
Weiskopf, Daniela, "Comprehensive analysis of dengue virus-specific responses supports an HLA-linked protective role for CD8+ T cells," PNAS, vol. 110, No. 22, pp. E2046-E2053 (2013).

European Search Report, Application No. EP 14 30 5984, dated Dec. 2, 2014.

International Search Report, Application No. PCT/EP2015/064010, dated Oct. 1, 2015.

* cited by examiner

Figure 1


Selected regions
NS 3
NS 4A
NS 4B
NS 5
A
B
CD8+ T-cell epitopes and T-cell response (Elispot)
1
2
3
4
Intra-serotype
Inter-serotype
Amino acid sequence conservation (10 amino acid window)
100%
90%
80%
60%
40%
4520
5120
5720
6320
6920
7520
8120
8720
9320
9920
10520
Genome position (nt)

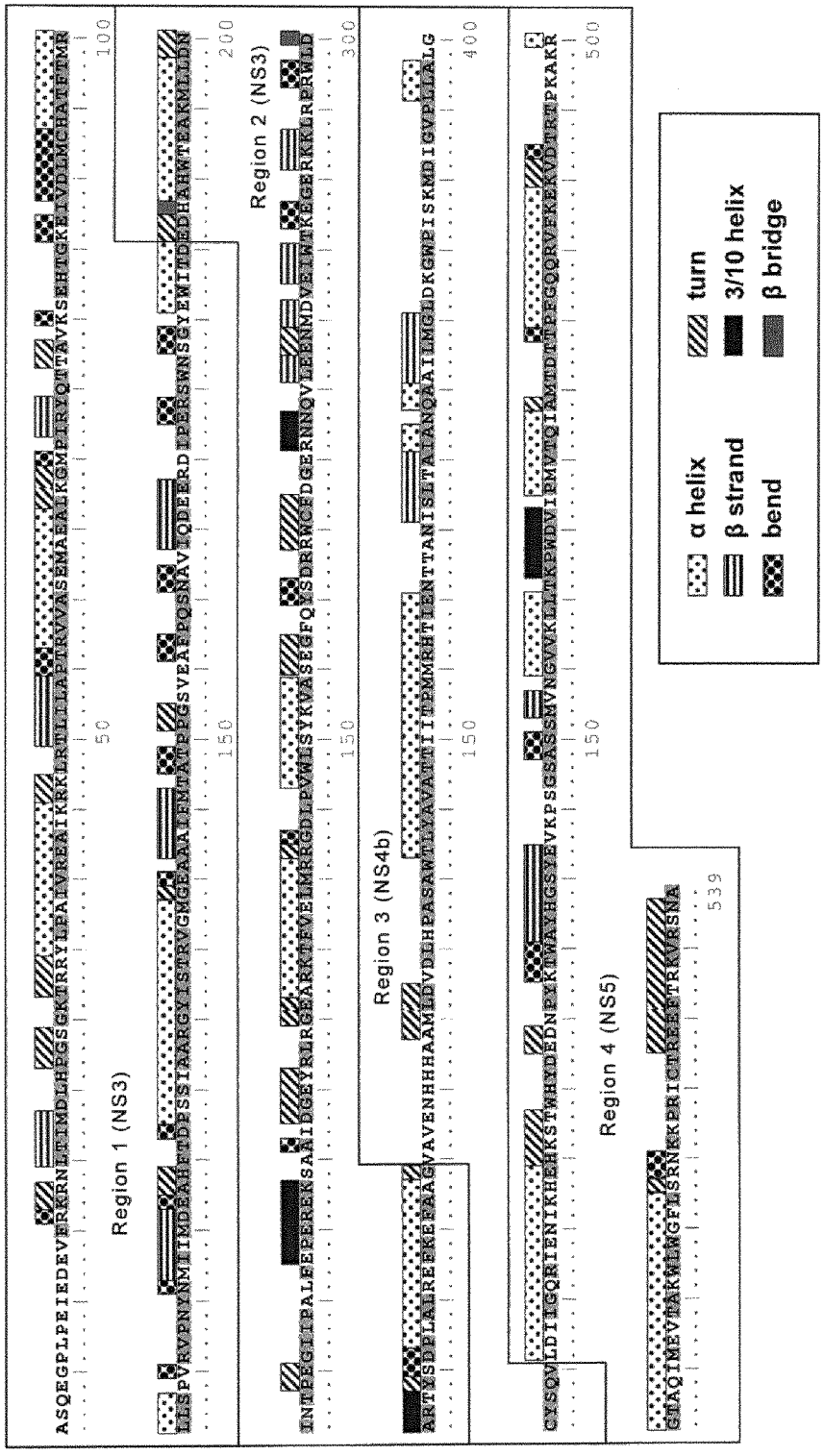

Region 1 (NS3)
Region 2 (NS3)
Region 3 (NS4b)
Region 4 (NS5)
α helix
β strand
bend
turn
3/10 helix
β bridge

Figure 2

- **Amino acid sequence of DENV2-NS polyepitope**

KSIEDNPEIEDDIFRKKRLTIMDLHPGAGKTKRYLPAIVREAIKRGLRTLILAPTRVVAAEMEEALRGLPIRYQ
TPAIRAEHTGREIVDLMCHATFTMRLLSPVRVPNYNLIIMDEAHFTDPASIAARGYISTRVEMGEAAGIFM
TATPPGSRDPFPQSNAPIMDEEREIPERSWNSGHEWVTDEDCAHWKEAKMLLDNINTPEGIIPSMFEPE
REKVDAIDGEYRLRGEARKTFVDLMRRGDLPVWLAYKVAAEGINYADRRWCFDGIKNNQILEENVEVEI
WTKEGERKKLKPRWLDARIYSDPLALKEFKEFAAGITTQESESNILDIDLRPASAWTLYAVATTFVTPMLRH
SIENSSVNVSLTAIANQATVLMGLGKGWPLSKMDIGVPLLAIGCYSQVLDIIGKRIEKIKQEHETSWHYDQ
DHPYKTWAYHGSYETKQTGSASSMVNGVVRLLTKPWDVVPMVTQMAMTDTTPFGQQRVFKEKVDTR
TQEPKEGTKKLMKITAEWLWKELGKKKTPRMCTREEFTRKVRSNA

- **Amino acid sequence of DENV3-NS polyepitope**

AEPDGPTPELEEEMFKKRNLTIMDLHPGSGKTRKYLPAIVREAIKRRLRTLILAPTRVVAAEMEEALKGLPIR
YQTTATKSEHTGREIVDLMCHATFTMRLLSPVRVPNYNLIIMDEAHFTDPASIAARGYISTRVGMGEAAAI
FMTATPPGTADAFPQSNAPIQDEERDIPERSWNSGNEWITDEDHAHWTEAKMLLDNINTPEGIIPALFE
PEREKSAAIDGEYRLKGESRKTFVELMRRGDLPVWLAHKVASEGIKYTDRKWCFDGQRNNQILEENMDV
EIWTKEGEKKKLRPRWLDARTYSDPLALKEFKDFAAGEPGVVSPTSYLDVDLHPASAWTLYAVATTVITP
MLRHTIENSTANVSLAAIANQAVVLMGLDKGWPISKMDLGVPLLALGCYSQVMDVIGERIKRIKEEHNST
WHYDDENPYKTWAYHGSYEVKATGSASSMINGVVKLLTKPWDVVPMVTQMAMTDTTPFGQQRVFK
EKVDTRTPRSMPGTRRVMGITAEWLWRTLGRNKKPRLCTREEFTKKVRTNA

- **Amino acid sequence of DENV4-NS polyepitope**

RIGEPDYEVDEDIFRKKRLTIMDLHPGAGKTKRILPSIVREALKRRLRTLILAPTRVVAAEMEEALRGLPIRYQ
TPAVKSEHTGREIVDLMCHATFTTRLLSSTRVPNYNLIVMDEAHFTDPSSVAARGYISTRVEMGEAAAIF
MTATPPGATDPFPQSNSPIEDIEREIPERSWNTGFDWITDEDHAHWTEAKMLLDNIYTPEGIIPTLFGPER
EKTQAIDGEFRLRGEQRKTFVELMRRGDLPVWLSYKVASAGISYKDREWCFTGERNNQILEENMEVEIW
TREGEKKKLRPRWLDARVYADPMALKDFKEFASGVKTETTILDVDLRPASAWTLYAVATTILTPMLRHTIE
NTSANLSLAAIANQAAVLMGLGKGWPLHRMDLGVPLLAMGCYSQVMTIIGRRLQRLQEEHKETWHYD
QENPYRTWAYHGSYEAPSTGSASSMVNGVVKLLTKPWDVIPMVTQLAMTDTTPFGQQRVFKEKVDTR
TPQPKPGTRMVMTTTANWLWALLGKKKNPRLCTREEFISKVRSNA

Figure 3

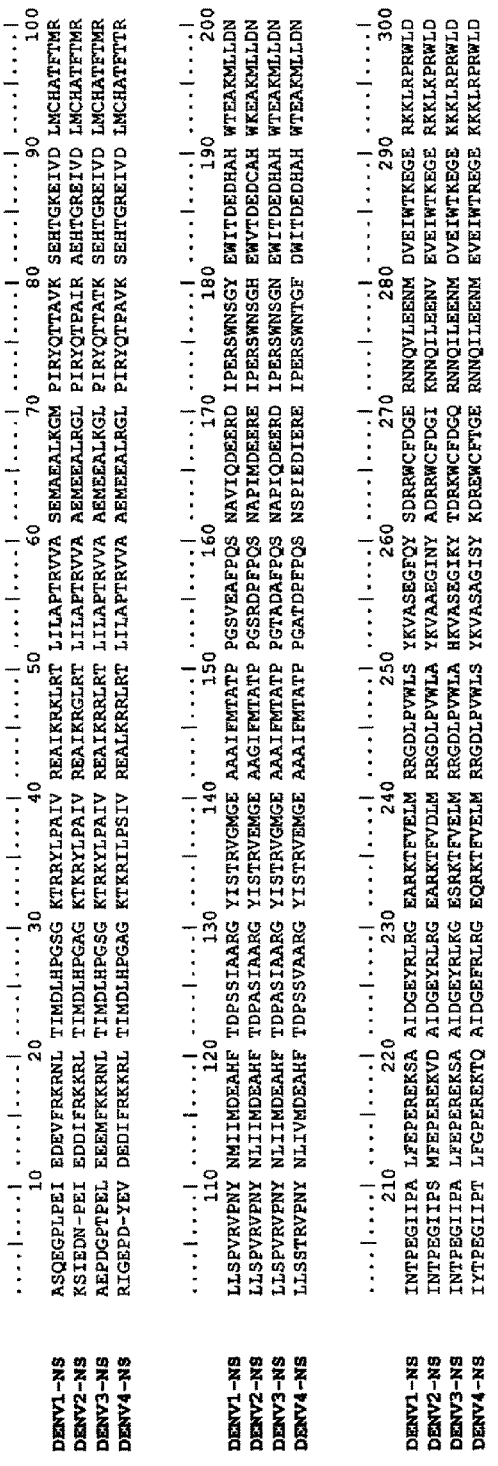
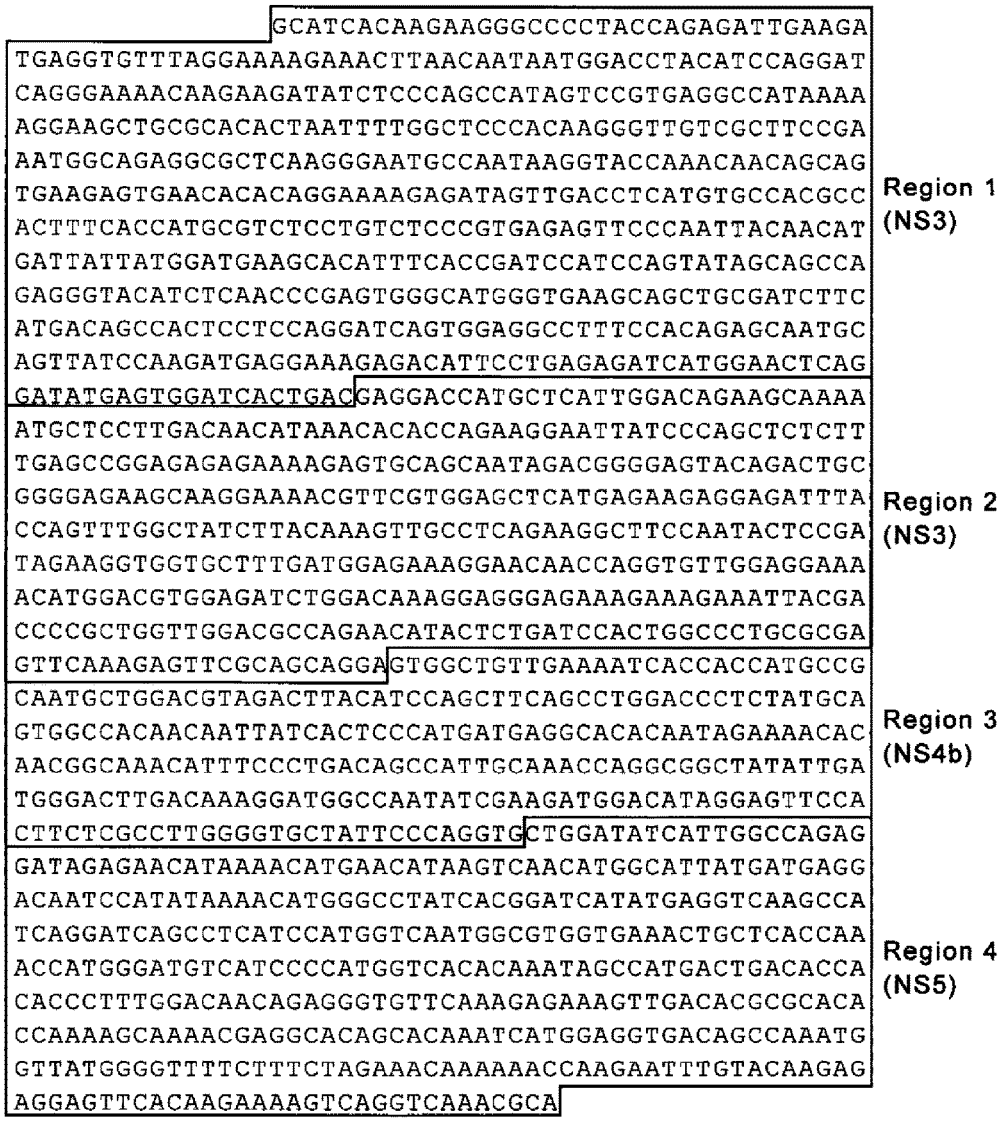


Figure 4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ATGACAGCCACTCCTCCAGGATCAGTGGAGGCCTTTCCACAGAGCAATGC
AGTTATCCAAGATGAGGAAAGAGACATTCCTGAGAGATCATGGAACTCAG
GATATGAGTGGATCACTGACGAGGACCATGCTCATTGGACAGAAGCAAAA
ATGCTCCTTGACAACATAAACACACCAGAAGGAATTATCCCAGCTCTCTT
TGAGCCGGAGAGAGAAAAGAGTGCAGCAATAGACGGGGAGTACAGACTGC
GGGGAGAAGCAAGGAAAACGTTCGTGGAGCTCATGAGAAGAGGAGATTTA
CCAGTTTGGCTATCTTACAAAGTTGCCTCAGAAGGCTTCCAATACTCCGA
TAGAAGGTGGTGCTTTGATGGAGAAAGGAACAACCAGGTGTTGGAGGAAA
ACATGGACGTGGAGATCTGGACAAAGGAGGGAGAAAGAAAGAAATTACGA
CCCCGCTGGTTGGACGCCAGAACATACTCTGATCCACTGGCCCTGCGCGA
GTTCAAAGAGTTCGCAGCAGGAGTGGCTGTTGAAAATCACCACCATGCCG
CAATGCTGGACGTAGACTTACATCCAGCTTCAGCCTGGACCCTCTATGCA
GTGGCCACAACAATTATCACTCCCATGATGAGGCACACAATAGAAAACAC
AACGGCAAACATTTCCCTGACAGCCATTGCAAACCAGGCGGCTATATTGA
TGGGACTTGACAAAGGATGGCCAATATCGAAGATGGACATAGGAGTTCCA
CTTCTCGCCTTGGGGTGCTATTCCCAGGTGCTGGATATCATTGGCCAGAG
GATAGAGAACATAAAACATGAACATAAGTCAACATGGCATTATGATGAGG
ACAATCCATATAAAACATGGGCCTATCACGGATCATATGAGGTCAAGCCA
TCAGGATCAGCCTCATCCATGGTCAATGGCGTGGTGAAACTGCTCACCAA
ACCATGGGATGTCATCCCCATGGTCACACAAATAGCCATGACTGACACCA
CACCCTTTGGACAACAGAGGGTGTTCAAAGAGAAAGTTGACACGCGCACA
CCAAAAGCAAAACGAGGCACAGCACAAATCATGGAGGTGACAGCCAAATG
GTTATGGGGTTTTCTTTCTAGAAACAAAAAACCAAGAATTTGTACAAGAG
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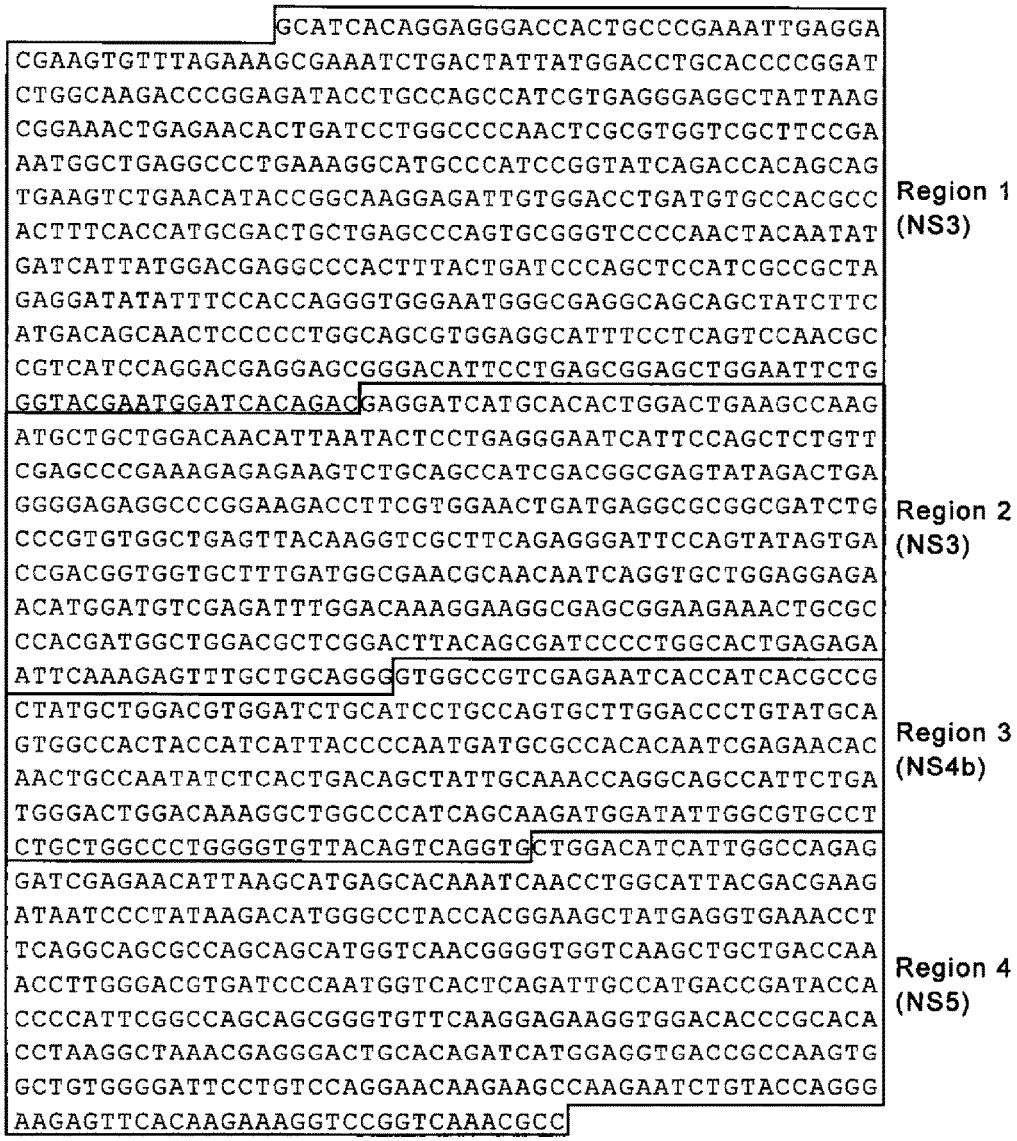
Region 1 (NS3)
Region 2 (NS3)
Region 3 (NS4b)
Region 4 (NS5)

Figure 5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CTGGCAAGACCCGGAGATACCTGCCAGCCATCGTGAGGGAGGCTATTAAG
CGGAAACTGAGAACACTGATCCTGGCCCCAACTCGCGTGGTCGCTTCCGA
AATGGCTGAGGCCCTGAAAGGCATGCCCATCCGGTATCAGACCACAGCAG
TGAAGTCTGAACATACCGGCAAGGAGATTGTGGACCTGATGTGCCACGCC
ACTTTCACCATGCGACTGCTGAGCCCAGTGCGGGTCCCCAACTACAATAT
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CCCGTGTGGCTGAGTTACAAGGTCGCTTCAGAGGGATTCCAGTATAGTGA
CCGACGGTGGTGCTTTGATGGCGAACGCAACAATCAGGTGCTGGAGGAGA
ACATGGATGTCGAGATTTGGACAAAGGAAGGCGAGCGGAAGAAACTGCGC
CCACGATGGCTGGACGCTCGGACTTACAGCGATCCCCTGGCACTGAGAGA
ATTCAAAGAGTTTGCTGCAGGGGTGGCCGTCGAGAATCACCATCACGCCG
CTATGCTGGACGTGGATCTGCATCCTGCCAGTGCTTGGACCCTGTATGCA
GTGGCCACTACCATCATTACCCCAATGATGCGCCACACAATCGAGAACAC
AACTGCCAATATCTCACTGACAGCTATTGCAAACCAGGCAGCCATTCTGA
TGGGACTGGACAAAGGCTGGCCCATCAGCAAGATGGATATTGGCGTGCCT
CTGCTGGCCCTGGGGTGTTACAGTCAGGTGCTGGACATCATTGGCCAGAG
GATCGAGAACATTAAGCATGAGCACAAATCAACCTGGCATTACGACGAAG
ATAATCCCTATAAGACATGGGCCTACCACGGAAGCTATGAGGTGAAACCT
TCAGGCAGCGCCAGCAGCATGGTCAACGGGGTGGTCAAGCTGCTGACCAA
ACCTTGGGACGTGATCCCAATGGTCACTCAGATTGCCATGACCGATACCA
CCCCATTCGGCCAGCAGCGGGTGTTCAAGGAGAAGGTGGACACCCGCACA
CCTAAGGCTAAACGAGGGACTGCACAGATCATGGAGGTGACCGCCAAGTG
GCTGTGGGGATTCCTGTCCAGGAACAAGAAGCCAAGAATCTGTACCAGGG
AAGAGTTCACAAGAAAGGTCCGGTCAAACGCC
Region 1 (NS3)
Region 2 (NS3)
Region 3 (NS4b)
Region 4 (NS5)

Figure 6

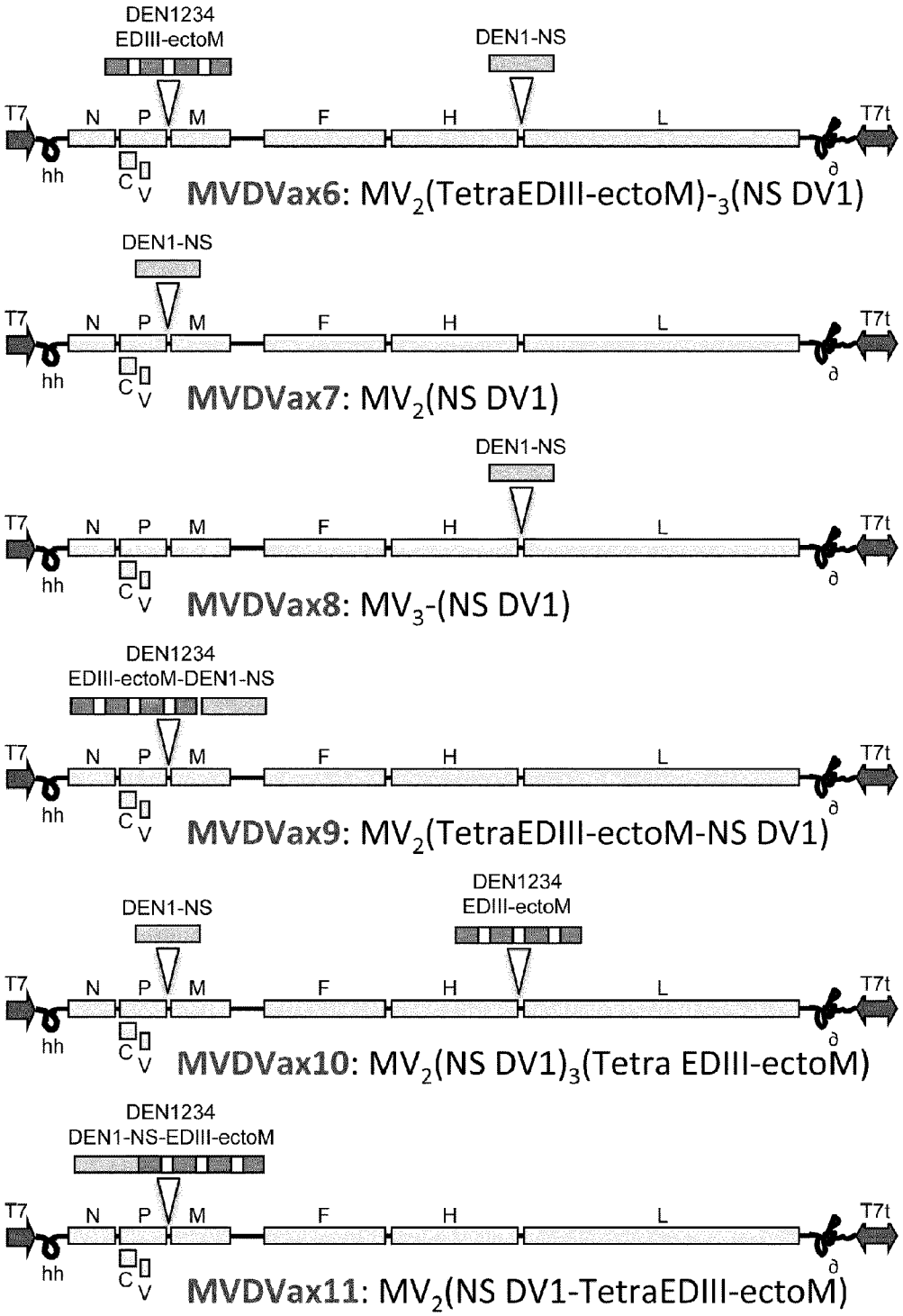
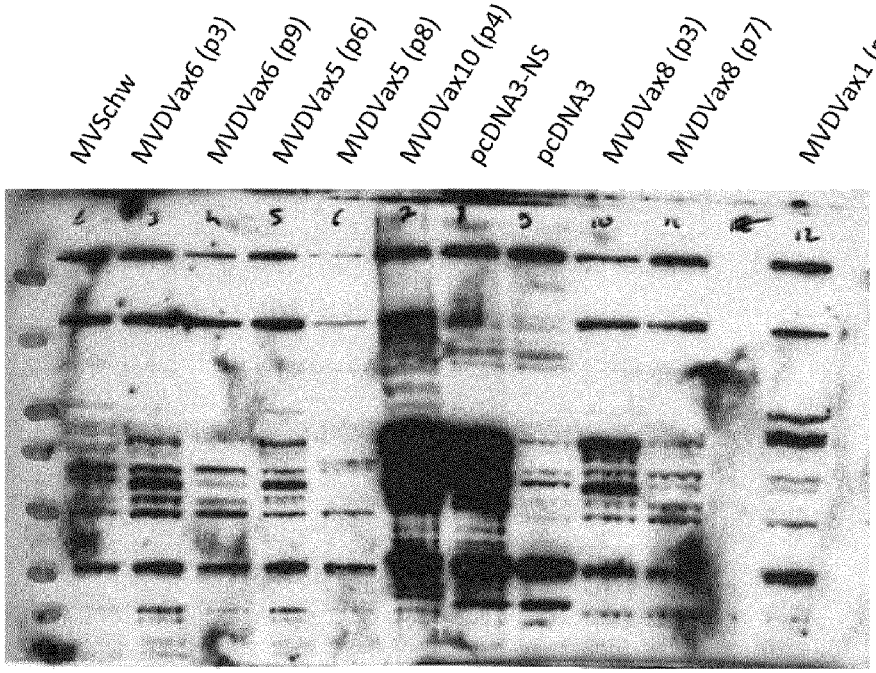
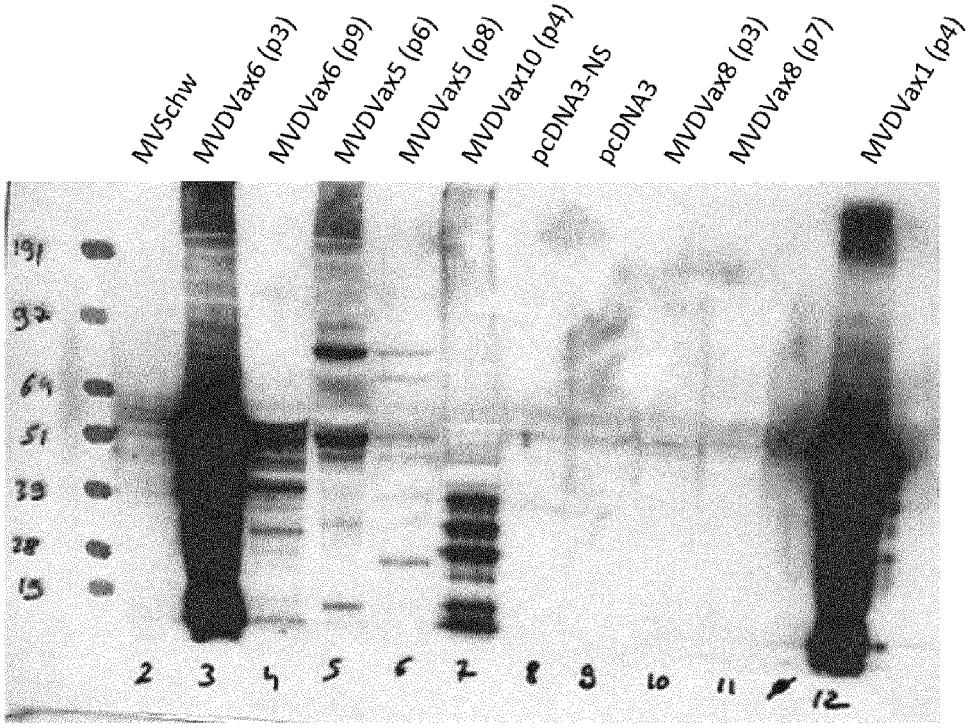

DEN1234
EDIII-ectoM
DEN1-NS
T7
N
P
M
F
H
L
T7t
hh
C
V
MVDVax6: MV2(TetraEDIII-ectoM)-3(NS DV1)
DEN1-NS
MVDVax7: MV2(NS DV1)
DEN1-NS
MVDVax8: MV3-(NS DV1)
DEN1234
EDIII-ectoM-DEN1-NS
MVDVax9: MV2(TetraEDIII-ectoM-NS DV1)
DEN1-NS
DEN1234
EDIII-ectoM
MVDVax10: MV2(NS DV1)3(Tetra EDIII-ectoM)
DEN1234
DEN1-NS-EDIII-ectoM
MVDVax11: MV2(NS DV1-TetraEDIII-ectoM)

Figure 7



Anti-NS3 DV1 (1/300)



Anti-EDIII DV1 (4E11, 1/1000)

Figure 8

Peptide	Sequence	
1	VKSEHTGKEIVDLMC	Pool 1
2	HTGKEIVDLMCHATF	
3	EIVDLMCHATFTMRL	
4	LMCHATFTMRLLSPV	
5	ATFTMRLLSPVRVPN	
6	MRLLSPVRVPNYNMI	
7	EFKEFAAGVAVENHH	
8	FAAGVAVENHHHAAM	
9	VAVENHHHAAMLDVD	
10	NHHHAAMLDVDLHPA	
11	AAMLDVDLHPASAWT	
12	DVDLHPASAWTLYAV	
13	HPASAWTLYAVATTI	
14	AWTLYAVATTIITPM	
15	YAVATTIITPMMRHT	
16	TTIITPMMRHTIENT	
17	TPMMRHTIENTTANI	
18	RHTIENTTANISLTA	
19	ENTTANISLTAIANQ	
20	ANISLTAIANQAAIL	
21	GWPISKMDIGVPLLA	Pool 2
22	SKMDIGVPLLALGCY	
23	IGVPLLALGCYSQVL	
24	DEDNPYKTWAYHGSY	
25	PYKTWAYHGSYEVKP	
26	WAYHGSYEVKPSGSA	
27	GSYEVKPSGSASSMV	
28	VKPSGSASSMVNGVV	
29	GSASSMVNGVVKLLT	
30	SMVNGVVKLLTKPWD	
31	GVVKLLTKPWDVIPM	
32	LLTKPWDVIPMVTQI	
33	PWDVIPMVTQIAMTD	
34	IPMVTQIAMTDTTPF	
35	TQIAMTDTTPFGQQR	
36	MTDTTPFGQQRVFKE	
37	FTMRLLSPV	
38	VAVENHHHAAM	
39	LYAVATTII	
40	TAIANQAAI	
41	SSMVNGVVKL	

Figure 9

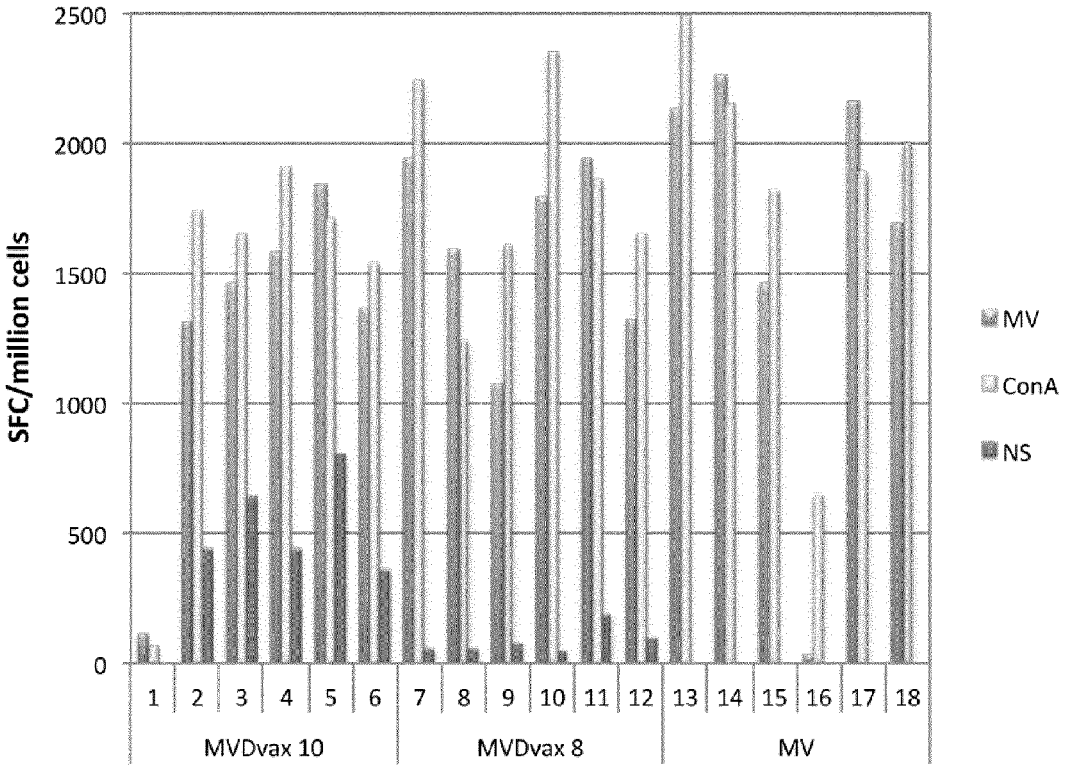

2500
2000
1500
1000
500
0
SFC/million cells
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
MVDvax 10
MVDvax 8
MV
MV
ConA
NS

Figure 10

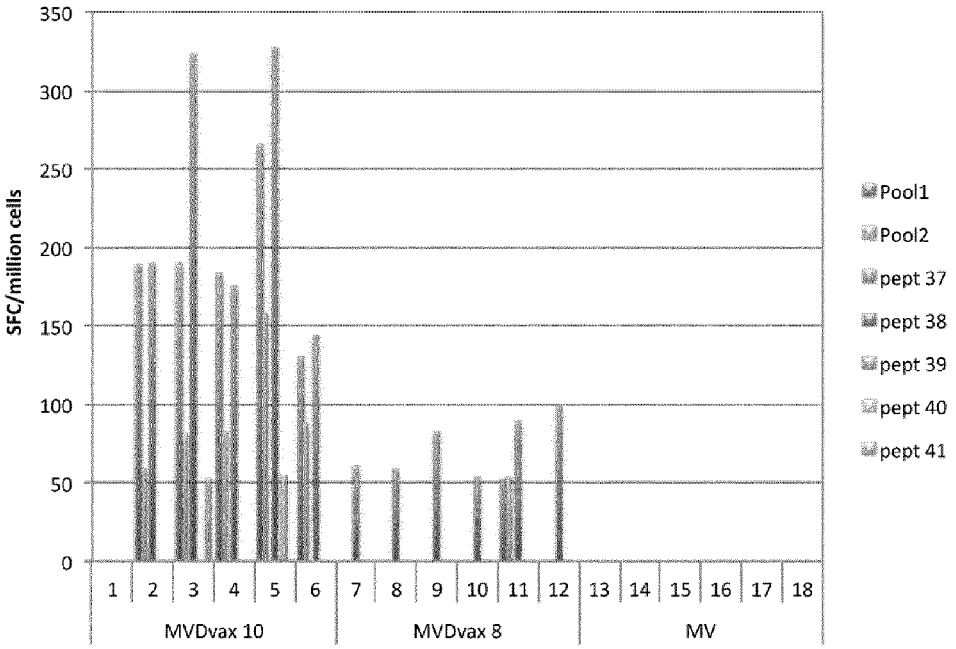


Figure 11

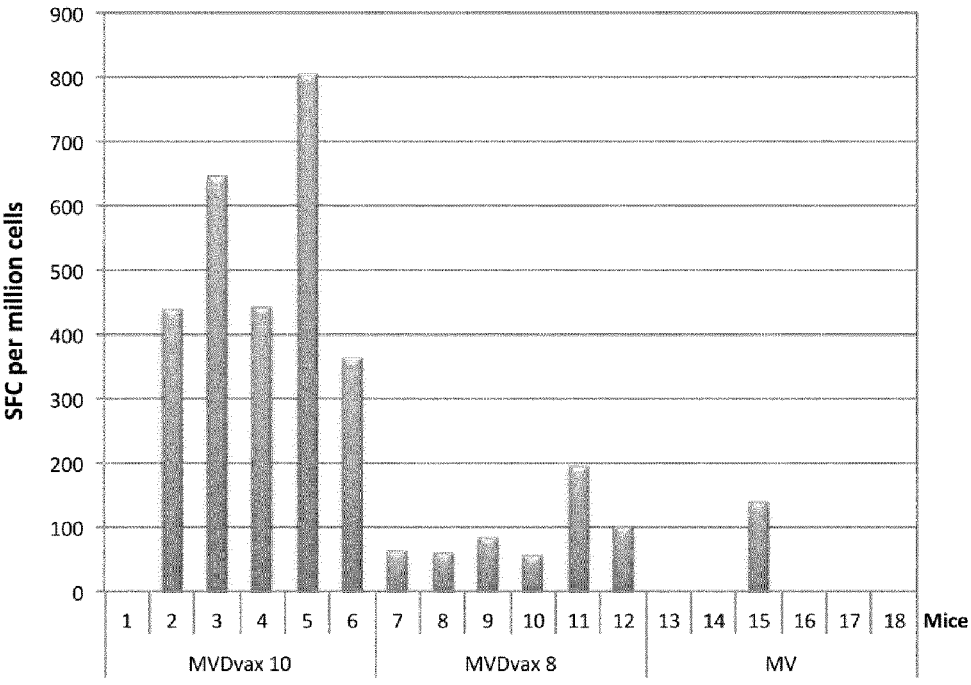


Figure 12

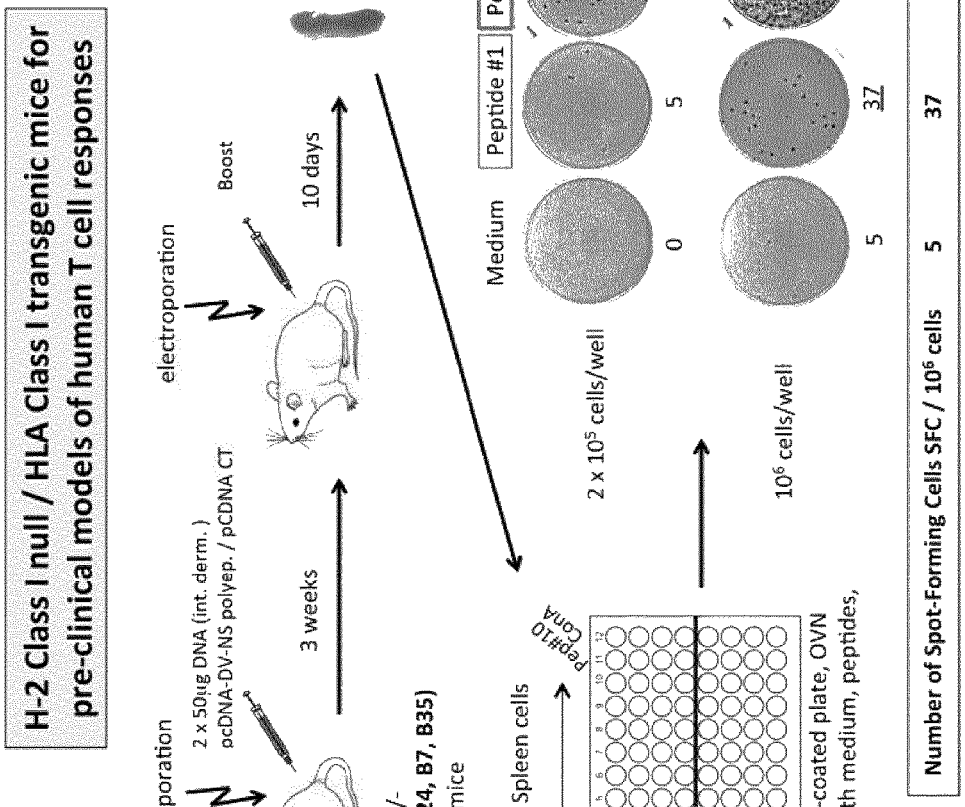
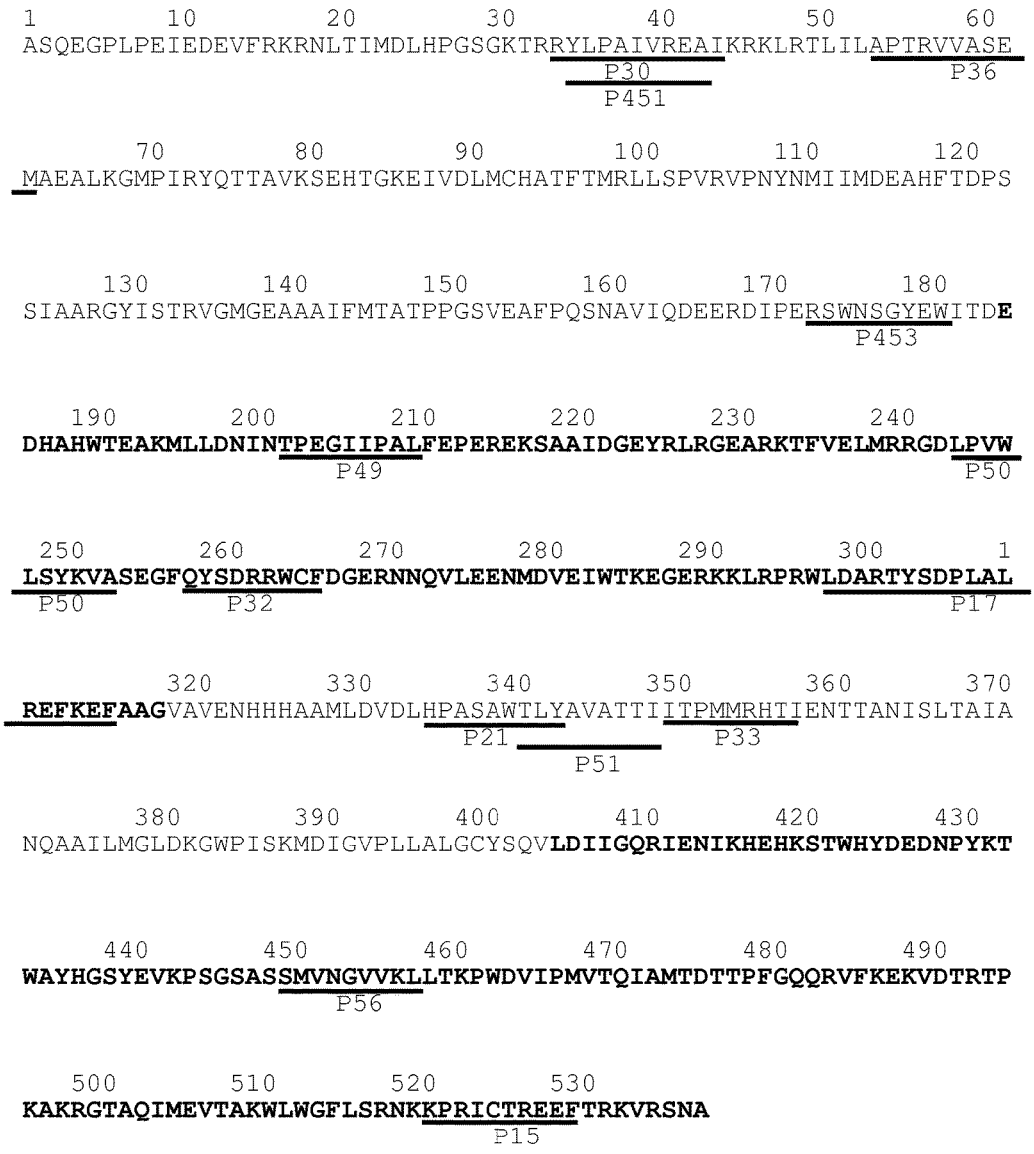

H-2 Class I null / HLA Class I transgenic mice for pre-clinical models of human T cell responses
electroporation
2 x 50µg DNA (int. derm.)
pcDNA-DV-NS polyep. / pCDNA CT
3 weeks
electroporation
Boost
10 days
Spleen
H-2 Class I -/-
HLA-(A2, A24, B7, B35)
Transgenic mice
Spleen cells
Medium
Pep#1
Pep#10
ConA
2 x 10^5 cells/well
10^6 cells/well
Anti-IFN-g-coated plate, OVN culture with medium, peptides, or ConA
Medium
Peptide #1
Peptide #2
ConA
0
5
174
301
5
37
511
210
Number of Spot-Forming Cells SFC / 10^6 cells
5
37
870
1505

Figure 13



	Epitopes / HLA restriction
1-185 Region 1 (NS3)	P30, P451, P56 / HLA-A2
186-319 Region 2 (NS3)	P17, P32, P33 / HLA-A24
320-405 Region 3 (NS4b)	P15, P30, P36 / HLA-B7
406-539 Region 4 (NS5)	P21, P49, P50, P51, P453 / HLA-B35

Figure 14

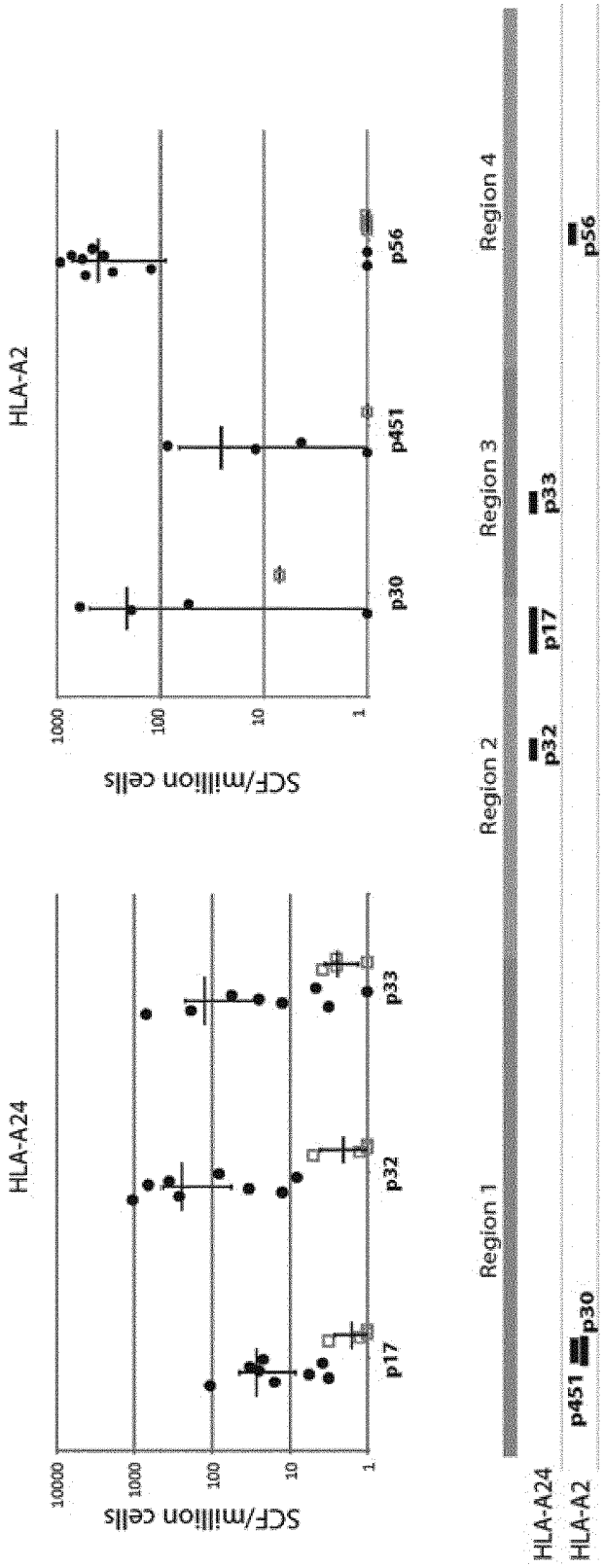

HLA-A24
SCF/million cells
10000
1000
100
10
1
p17
p32
p33
HLA-A2
SCF/million cells
1000
100
10
1
p30
p451
p56
Region 1
Region 2
Region 3
Region 4
HLA-A24
HLA-A2
p451
p30
p32
p17
p33
p56

Figure 15A

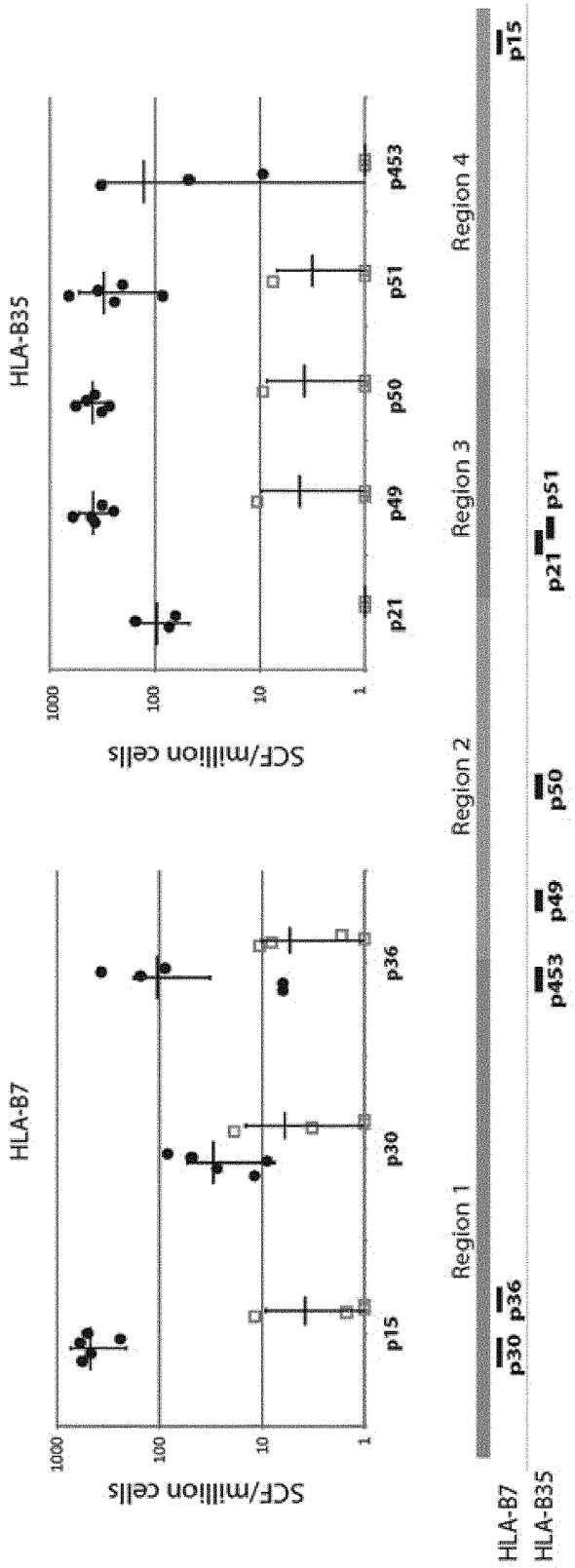

HLA-B7
SCF/million cells
1000
100
10
1
p15
p30
p36
HLA-B35
SCF/million cells
1000
100
10
1
p21
p49
p50
p51
p453
HLA-B7
HLA-B35
Region 1
Region 2
Region 3
Region 4
p30
p36
p453
p49
p50
p21
p51
p15

Figure 15B

Figure 16A

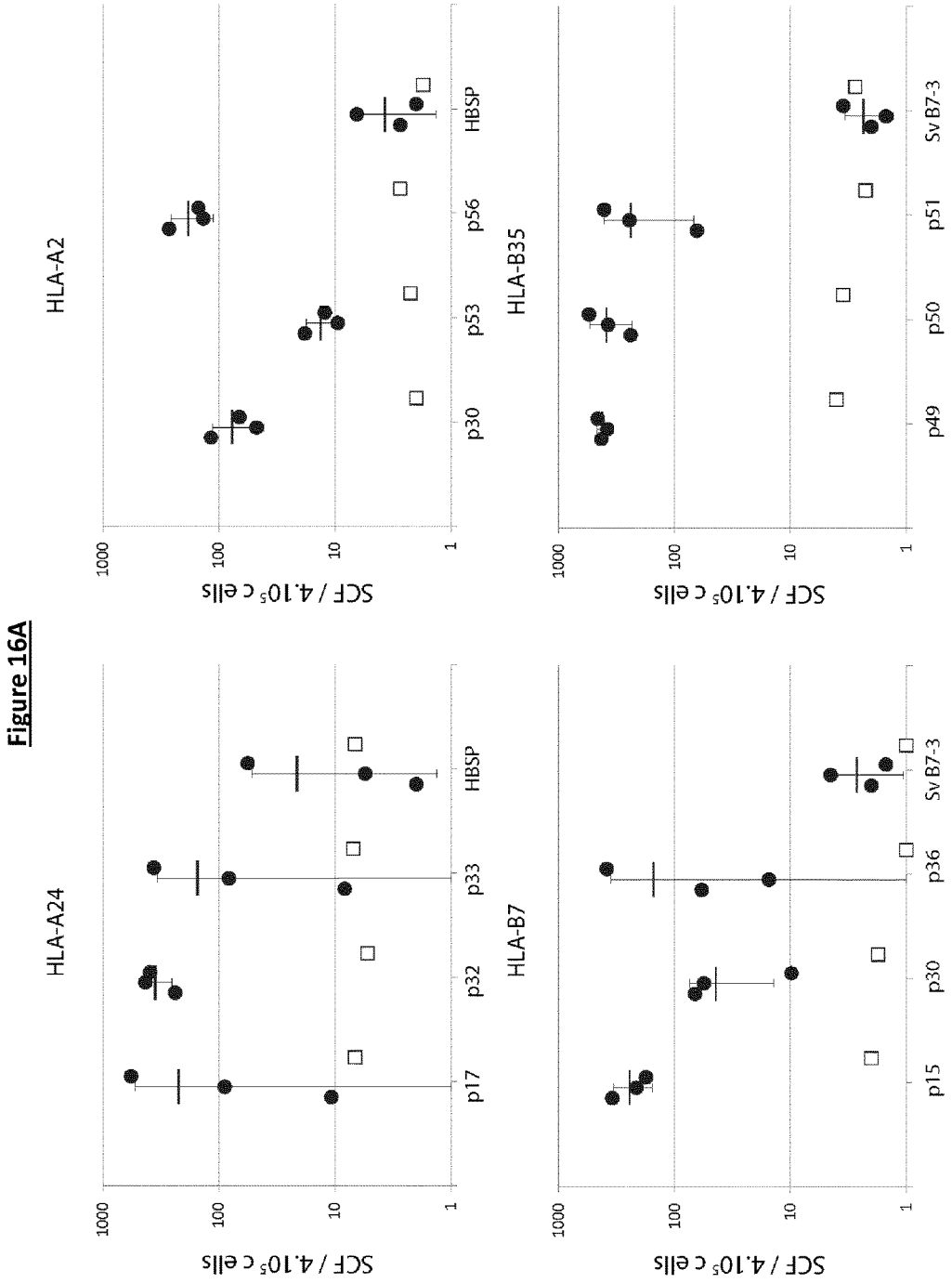
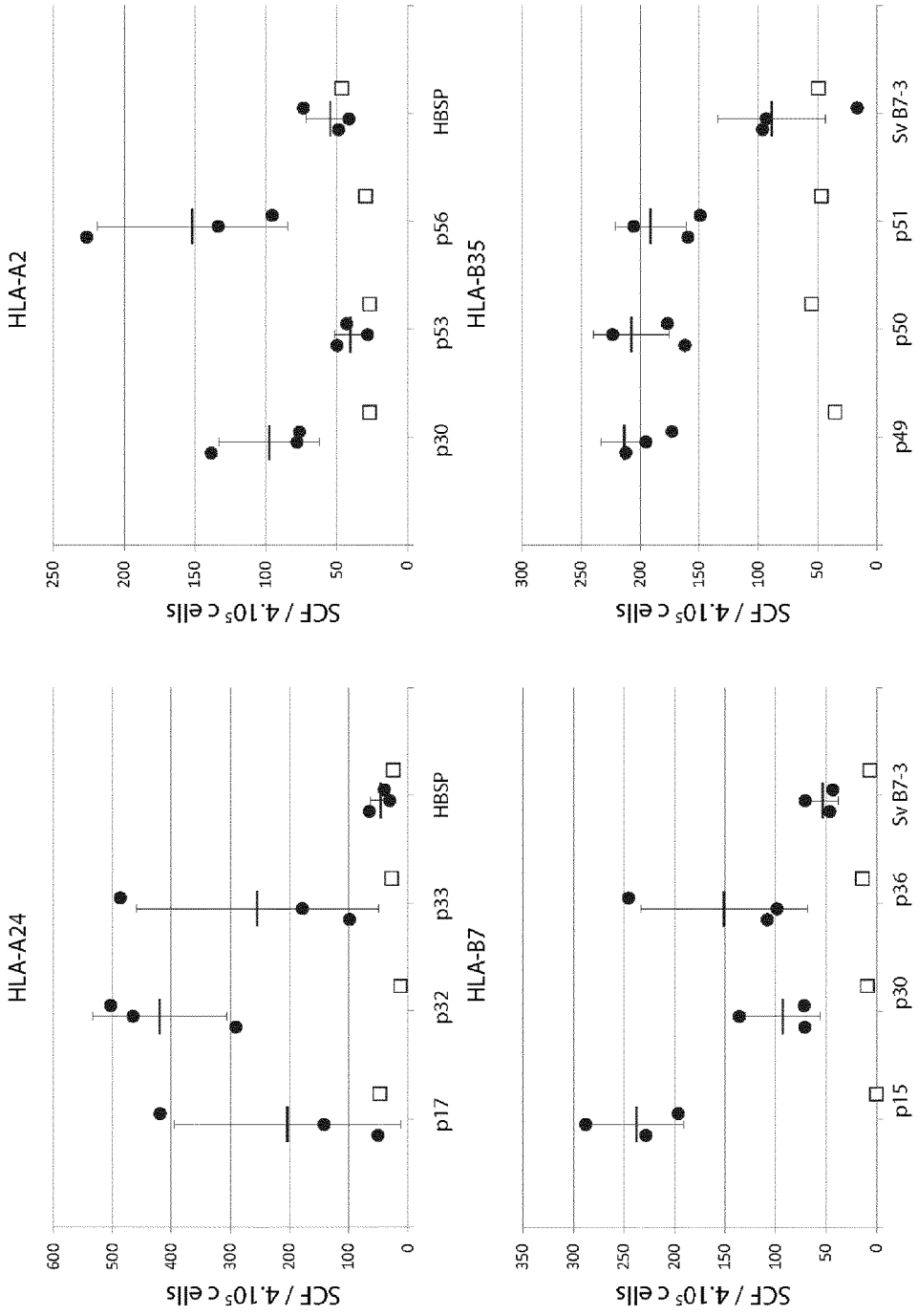

HLA-A24
HLA-A2
HLA-B7
HLA-B35
SCF / 4.10^5 cells
1000
100
10
1
p17
p32
p33
HBSP
p30
p53
p56
p15
p36
p49
p50
p51
Sv B7-3

Figure 16B


HLA-A2
HLA-B35
HLA-A24
HLA-B7
SCF / 4.10^5 cells
p30
p53
p56
HBSP
p49
p50
p51
Sv B7-3
p17
p32
p33
p15
p30
p36

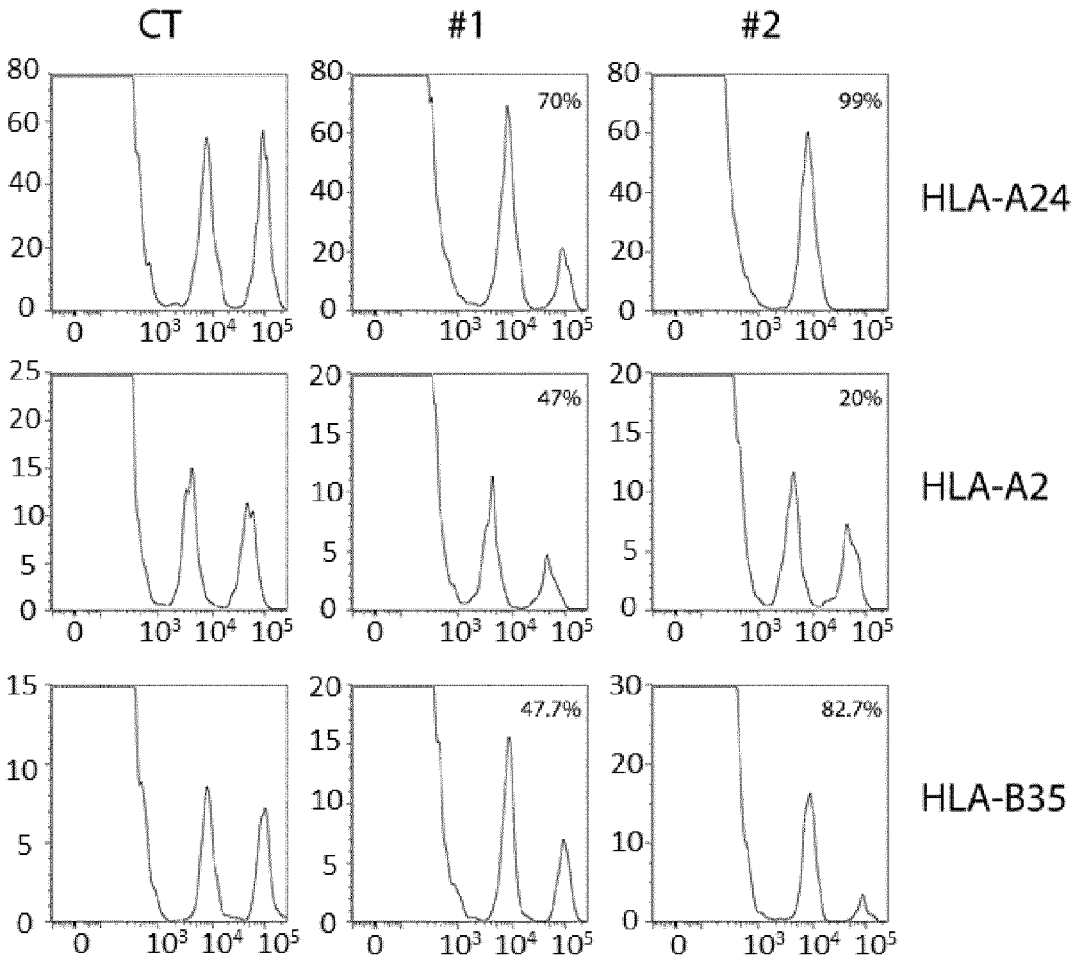


Figure 17

Nb	HLA RESTRICTION (REFERENCES)	PEPTIDE SYNTHESIZED[a, b]	POSITION	+ SFC[c]
P20	B35 (5)	LPEIEDEVF	NS3-1 (7-15)	-
P19	B35 (5, 9)	HPGSGKTRRY	NS3-1 (26-35)	-
P30	A31 (1, 7), B7 (6, 9)	RYLPAIVREAI	NS3-1 (34-44)	B7
P451	A2 (10)	YLPAIVREA	NS3-1 (35-43)	A2
P11	A31 (1, 7), B7 (6, 9)	LPAIVREAI	NS3-1 (36-44)	-
P36	B7 (1, 2, 9), B35 (9)	APTRVVASEM	NS3-1 (54-63)	B7
P48	B7 (1, 9), A2,11; B35,62 (3)	EMAEALKGMPIRYQT	NS3-1 (62-76)	-
P12	ND (2), B7 (9)	SPVRVPNYNM	NS3-1 (103-112)	-
P454	B7 (10)	VPNYNMIIM	NS3-1 (107-115)	-
P18	ND (2), B35 (5, 9)	DPSSIAARGY	NS3-1 (122-131)	-
P457	B7 (10)	AVIQDEERDI	NS3-1 (162-171)	-
P453	B58 (1, 7)	RSWNSGYEW	NS3-1 (174-182)	B35
P49	B35 (1, 2, 3, 4, 9)	TPEGIIPAL	NS3-2 (203-211)	B35
P28	A11 (9)	KTFVELMRR	NS3-2 (234-242)	NT
P2	B55 (1), A2 (9)	ELMRRGDLPV	NS3-2 (238-247)	-
P450	A2 (10)	DLMRRGDLPV	NS3-2 (238-247)	-
P50	nd (2), B35 (5)	LPVWLSYKVA	NS3-2 (245-254)	B35
P32	A24 (1, 2, 6, 9, 11)	QYSDRRWCF	NS3-2 (259-267)	A24
P73	A24 (1, 2, 6, 11)	NYADRRWCF	NS3-2 (259-267)	NT
P74	A24 (13)	NYADRKWCF	NS3-2 (259-267)	NT
P75	A24 (13)	KYTDRKWCF	NS3-2 (259-267)	NT
P76	A24 (13)	SYKDREWCF	NS3-2 (259-267)	NT
P35	B7 (8, 9)	RPRWLDART	NS3-2 (295-303)	-
P17	A24 (1, 7, 8)	LDARTYSDPLALREFKEF	NS3-2 (299-316)	A24
P29	A24 (1, 7, 8)	RIYSDPLALK	NS3-2 (302-311)	-

TO FIG. 18 (CONT.)

FIG. 18

TO FIG. 18 (CONT.)

FROM FIG. 18

FROM FIG. 18

P452	A11, A24 (1, 7, 8)	RTYSDPLALR	NS3-2 (302-311)	NT
P21	B7, B35 (9)	HPASAWTLY	NS4b (336-344)	B35
P16	B7, B35 (9)	PASAWTLY	NS4b (337-344)	-
P13	B35 (9)	HPASAWTLYA	NS4b (336-345)	NT
P51	A2 (6) B35 (9)	TLYAVATTI	NS4b (342-350)	B35
P52	B35 (9)	VATTIITPM	NS4b (346-354)	-
P33	A24 (9)	ITPMMRHTI	NS4b (351-359)	A24
P14	A24 (9)	TPMMRHTIEN	NS4b (352-361)	-
P22	B35 (5, 9)	IANQAAILM	NS4b (371-379)	-
P456	A11 (10)	AAILMGLDK	NS4b (375-383)	NT
P53	A2 (6)	KMDIGVPLL	NS4b (389-397)	-
P54	B35 (9)	VPLLALGCY	NS4b (394-402)	-
P55	A2,11, B35,62 (3)	DNPYKTWAYH	NS5 (429-438)	-
P24	B35 (9)	WAYHGSYEV	NS5 (435-443)	-
P56	A2 (6)	SMVNGVVKL	NS5 (435-443)	A2
P5	B55 (1), A2,24, B55,61 (3), A2 (8)	LLTKPWDVIPMVTQI	NS5 (459-473)	-
P6	"	LLTKPWDVIP	NS5 (459-468)	-
P7	"	LTKPWDVIPM	NS5 (460-469)	-
P8	"	TKPWDVIPMV	NS5 (461-470)	-
P9	"	KPWDVIPMVT	NS5 (462-471)	-
P10	"	PWDVIPMVTQ	NS5 (463-472)	-
P27	"	WDVIPMVTQI	NS5 (464-473)	-
P455	B7 (9)	IPMVTQIAM	NS5 (467-475)	-
P34	A68, B35 (1)	DTTPFGQQR	NS5 (477-485)	-
P23	B35 (9)	TPFGQQRVF	NS5 (479-487)	-

TO FIG. 18 (CONT. 2)

TO FIG. 18 (CONT. 2)

FIG. 18 (CONT.)

FROM FIG. 18 (CONT.)

FROM FIG. 18 (CONT.)

P3	A2,32, B35,62 (3), B7 (7, 8)	TAKWLWGFLSRNKKPRICTR	NS5 (509-528)	-
P4	A2,32, B35,62 (3)	WGFLSRNKK	NS5 (514-522)	-
P15	B7 (5, 8, 9)	KPRICTREEF	NS5 (522-531)	B7

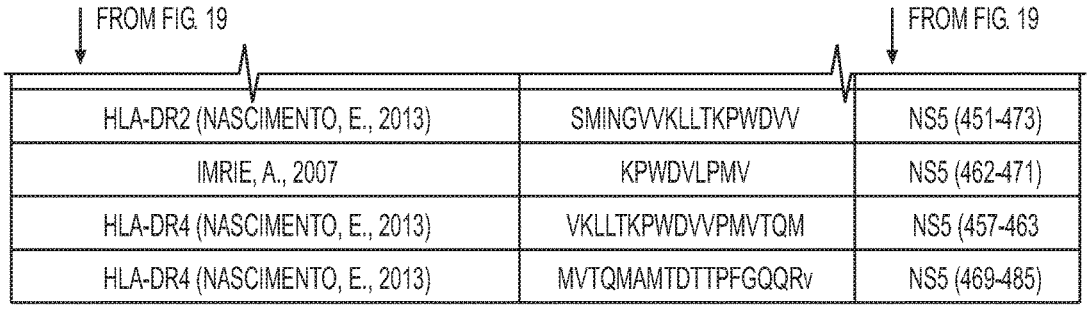
FIG. 18 (CONT. 2)

HLA CLASS II RESTRICTION (REFERENCES)	PEPTIDE SEQUENCE	POSITION
HLA-DR2 (NASCIMENTO, E., 2013)	PELEEEMFKKRNLTI	NS3-1 (8-22)
MALOY M. MANGADA, 2005	RKLTIMDLHPGSGKT	NS3-1 (18-32)
HLA-DR15 (SIMMONS, ET AL., 2006)	TKRYLPPAIVREAIKR	NS3-1 (32-46)
HLA-DR15 (ZENG, L., ET AL., 1996)	RKYLPAIVRE	NS3-1 (33-42)
HLA-DR3 (NASCIMENTO, E., 2013)	LPAIVREAIKRRLRT	NS3-1 (36-50)
HLA-DR3 (NASCIMENTO, E., 2013)	VREAIKRRLRTLILA	NS3-1 (40-54)
HLA-DR15 (KURANE, I., 1998)	TRVVAAEMEEA	NS3-1 (56-66)
HLA-DRB1*15:01 (MALOY M. MANGADA, 2005)	PTRVVAAEMEEAMKG	NS3-1 (55-69)
HLA-DR15 (MORAN, E., 2008)	ALKGMPIRYQTTAVK	NS3-1 (66-80
HLA-DR4 (NASCIMENTO, E., 2013)	KGLPIRYQTTATKSE	NS3-1 (68-82)
HLA-DR4 (NASCIMENTO, E., 2013)	IRYQTTATKSEHTGR	NS3-1 (72-86)
HLA-DPw2 (MALOY M. MANGADA, 2005)	HTGREIVDLMCHATE	NS3-1 (83-97)
HLA-DPA1*01:03/DPB1*02:01 (FALTA, MT., 2013)	REIVDLMCHATF	NS3-1 (86-97
HLA-DPw2 (KURANE, I., ET AL., 1993)	EIVDLMCHAT	NS3-1 (87-96)
HLA-DPw2 (OKAMOTO, Y., 1998)	VDLMCHATFT	NS3-1 (89-98)
HLA-DRB1*01:01 (WEISKOPF, D., 2013)	TFTMRLLSPVRVPNY	NS3-1 (96-110)
RIVINO, L., 2013	PNYNLIIMDEAHFTD	NS3-1 (108-122)
HLA-DR2 (NASCIMENTO, E., 2013)	ASIAARGYISTRVGM	NS3-1 (124-138)
HLA-DR4 (NASCIMENTO, E., 2013)	EAAAIFMTATPPGTA	NS3-1 (139-154)
MALOY M. MANGADA, 2005	REGEKKKLRPRWLDR	NS3-2 (287-301)
HLA-DR2 (NASCIMENTO, E., 2013)	PLALKEFKDFAAGRK	NS3-2 (307-319)
HLA-DR3 (NASCIMENTO, E., 2013)	KEEHSSTWHYDDENPYK	NS5 (417-433)
HLA-DR2 (NASCIMENTO, E., 2013)	TWHYDDENPYKTWAYHG	NS5 (423-439)
HLA-DR2 (NASCIMENTO, E., 2013)	DENPYKTWAYHGSYEVK	NS5 (427-444)
RIVINO ET AL., 2013	KTWAYHGSYETKQTG	NS5 (433-447)

TO FIG. 19 (CONT.)

FIG. 19

TO FIG. 19 (CONT.)



HLA-DR2 (NASCIMENTO, E., 2013)	SMINGVVKLLTKPWDVV	NS5 (451-473)
IMRIE, A., 2007	KPWDVLPMV	NS5 (462-471)
HLA-DR4 (NASCIMENTO, E., 2013)	VKLLTKPWDVVPMVTQM	NS5 (457-463
HLA-DR4 (NASCIMENTO, E., 2013)	MVTQMAMTDTTPFGQQRv	NS5 (469-485)

FIG. 19 (CONT.)

p30

NS POLYEPITOPE	R	Y	L	P	A	I	V	R	E	A	I
SEROTYPE 1	-	-	-	-	-	-	-	-	-	-	-
SEROTYPE 2	-	-	-	-	-	-	-	-	-	-	-
SEROTYPE 3	K	-	-	-	-	-	-	-	-	-	-
SEROTYPE 4	-	I	-	-	S	-	-	-	-	-	L

p451

NS POLYEPITOPE	Y	L	P	A	I	V	R	E	A
SEROTYPE 1	-	-	-	-	-	-	-	-	-
SEROTYPE 2	-	-	-	-	-	-	-	-	-
SEROTYPE 3	-	-	-	-	-	-	-	-	-
SEROTYPE 4	I	-	-	S	-	-	-	-	-

p56

NS POLYEPITOPE	S	M	V	N	G	V	V	K	L
SEROTYPE 1	-	-	-	-	-	-	-	K/R	-
SEROTYPE 2	-	-	-	-	-	-	-	R/K	-
SEROTYPE 3	-	-	I	-	-	-	-	-	-
SEROTYPE 4	-	-	-	-	-	-	-	-	-

FIG. 20A

p17

NS POLYEPITOPE	L	D	A	R	T	Y	S	D	P	L	A	L	R	E	F	K	E	F
SEROTYPE 1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SEROTYPE 2	-	-	-	-	I	-	-	-	-	-	-	-	K	-	-	-	-	-
SEROTYPE 3	K	-	-	-	-	-	-	-	-	-	-	-	K	-	-	-	D	-
SEROTYPE 4	-	I	-	-	V	-	A	-	-	M	-	-	K	D	-	-	-	-

p32

NS POLYEPITOPE	Q	Y	S	D	R	R	W	C	F
SEROTYPE 1	-	-	-	-	-	-	-	-	-
SEROTYPE 2	N	-	A	-	-	R/K	-	-	-
SEROTYPE 3	K	-	T	-	-	K	-	-	-
SEROTYPE 4	S	-	K	-	-	E	-	-	-

p33

NS POLYEPITOPE	I	T	P	M	M	R	H	T	I
SEROTYPE 1	-	-	-	-	-	-	-	-	-
SEROTYPE 2	V	-	-	-	L	-	-	S	-
SEROTYPE 3	-	-	-	-	L	-	-	-	-
SEROTYPE 4	L	-	-	-	L	-	-	-	-

FIG. 20B

p15

NS POLYEPITOPE	K	P	R	I	C	T	R	E	E	F
SEROTYPE 1	-	-	-	-	-	-	-	-	-	-
SEROTYPE 2	T	-	-	M	-	-	-	K/R	-	-
SEROTYPE 3	K/R	-	-	L	-	-	H	-	-	-
SEROTYPE 4	N	-	-	L	-	-	-	-	-	-

p30

NS POLYEPITOPE	R	Y	L	P	A	I	V	R	E	A	I
SEROTYPE 1	-	-	-	-	-	-	-	-	-	-	-
SEROTYPE 2	-	-	-	-	-	-	-	-	-	-	-
SEROTYPE 3	K	-	-	-	-	-	-	-	-	-	-
SEROTYPE 4	-	I	-	-	S	-	-	-	-	-	L

p36

NS POLYEPITOPE	A	P	T	R	V	V	A	S	E	M
SEROTYPE 1	-	-	-	-	-	-	-	-	-	-
SEROTYPE 2	-	-	-	-	-	-	-	A	-	-
SEROTYPE 3	-	-	-	-	-	-	-	A	-	-
SEROTYPE 4	-	-	-	-	-	-	-	A	-	-

FIG. 20C

p21

NS POLYEPITOPE	H	P	A	S	A	W	T	L	Y
SEROTYPE 1	H/R	-	-	-	-	-	-	-	-
SEROTYPE 2	R	-	-	-	-	-	-	-	-
SEROTYPE 3	-	-	-	-	-	-	-	-	-
SEROTYPE 4	R	-	-	-	-	-	-	-	-

p49

NS POLYEPITOPE	T	P	E	G	I	I	P	A	L
SEROTYPE 1	-	-	-	-	-	-	-	-	-
SEROTYPE 2	-	-	-	-	-	-	-	S	M
SEROTYPE 3	-	-	-	-	-	-	-	-	-
SEROTYPE 4	-	-	-	-	-	-	-	T	-

p50

NS POLYEPITOPE	L	P	V	W	L	S	Y	K	V	A
SEROTYPE 1	-	-	-	-	-	-	-	-	-	-
SEROTYPE 2	-	-	-	-	-	A	-	K/R	-	-
SEROTYPE 3	-	-	-	-	-	A	H	-	-	-
SEROTYPE 4	-	-	-	-	-	-	-	-	-	-

p51

NS POLYEPITOPE	T	L	Y	A	V	A	T	T	I
SEROTYPE 1	-	-	-	-	-	-	-	-	I/V
SEROTYPE 2	-	-	-	-	-	-	-	-	F
SEROTYPE 3	-	-	-	-	-	-	-	-	V
SEROTYPE 4	-	-	-	-	-	-	-	-	-

p453

NS POLYEPITOPE	R	S	W	N	S	G	Y	E	W
SEROTYPE 1	-	-	-	-	-	-	-	E/D	-
SEROTYPE 2	-	-	-	-	-	-	H	-	-
SEROTYPE 3	-	-	-	-	-	-	N	-	-
SEROTYPE 4	-	-	-	-	T	-	F	D	-

FIG. 20D

DENGUE VIRUS CHIMERIC POLYEPITOPE COMPOSED OF FRAGMENTS OF NON-STRUCTURAL PROTEINS AND ITS USE IN AN IMMUNOGENIC COMPOSITION AGAINST DENGUE VIRUS INFECTION

FIELD OF THE INVENTION

The present invention is directed to a dengue virus chimeric polyepitope composed of fragments of non-structural proteins and its use in an immunogenic composition against dengue virus infection. The present invention provides means, in particular polynucleotides, vectors, cells and methods to produce vectors expressing said chimeric polyepitopes, in particular vectors consisting of recombinant measles virus (also designated MV) particles. The present invention also relates to the use of the recombinant MV particles, in particular under the form of a composition or of a vaccine, for the prevention and/or treatment of a dengue virus infection.

BACKGROUND OF THE INVENTION

Dengue virus (DENV) belongs to the Flaviviridae family of enveloped, positive-strand RNA viruses, and is transmitted by *Aedes* mosquitoes. DENV infection is the most important arthropod-borne viral disease, with about 390 million infections every year, that can result in dengue fever (DF), and in 1-5% of cases in dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), characterized by vascular leak leading to hypotensive shock (World Health Organization (WHO) Press 2009, *WHO/HTM/NTD/DEN/* 2009. 1 ed.; Bhatt S et al., *Nature* 2013, 496(7446):504-507). Over 2 million cases of severe dengue disease and over 20,000 deaths are estimated to occur each year (Gubler D J, The American journal of tropical medicine and hygiene 2012, 86(5):743-744).

There are four main DENV serotypes (designated DENV1-4) that are 67-75% identical at the amino acid level. The viral RNA genome is translated as a single polyprotein that is cleaved by viral and host proteases into three structural proteins (capsid (C), premembrane (prM), and envelope (E)) and seven non-structural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5). Complete nucleotide sequences of the reference genomes of the 4 dengue virus serotypes can be accessed from the Genbank database under accession numbers NC_001477.1, NC_001474.2, NC_001475.2 and NC_002640.1 respectively. During infection, the E protein interacts with cellular receptors and viral uptake occurs via receptor-mediated endocytosis (Heinz F X et al., *Archives of virology Supplementum* 1994, 9:339-348; Mukhopadhyay S et al., *Nat Rev Microbiol* 2005, 3(1):13-22). The E protein is structurally conserved among flaviviruses and consists of three domains (EDI, EDII, and EDIII) (Rey F A et al., *Nature* 1995, 375(6529):291-298). Notably, the EDIII domain induces the most potent neutralizing and serotype-specific antibodies (Beltramello M et al., *Cell host & microbe* 2010, 8(3):271-283; Shrestha B et al., *PLoS Pathog* 2010, 6(4):e1000823; Sukupolvi-Petty S et al., *J Virol* 2010, 84(18):9227-9239; Wahala W M et al., *PLoS Pathog* 2010, 6(3):e1000821; de Alwis R et al, *PLoS neglected tropical diseases* 2011, 5(6):e1188; Yauch L E et al., *Advances in virus research* 2014, 88:315-372).

A single minimal tetravalent DENV antigen composed of the four envelope domain III (EDIII) from the four DENV serotypes fused to the ectodomain of the membrane protein (ectoM) has been previously described (Brandler et al., *PLoS* 2007, 1(3), e96; Brandler et al., *Vaccine,* 2010, 28, 6730-6739). When expressed by a replicating viral vector derived from live-attenuated MV vaccine, this antigen induced neutralizing antibodies against the four serotypes of dengue virus (Brandler et al., *Vaccine,* 2010, 28, 6730-6739). However, evaluated in a non-human primate model of DENV infection, a recombinant MV vector expressing the tetravalent EDIII-ectoM antigen provided only partial protection. This observation indicated that an additional DENV antigen was missing to provide full protection.

The NS proteins are involved in viral replication and assembly and are usually not incorporated in mature viral particles. Strikingly, while a primary infection by one DENV serotype induces a lasting protective immunity against reinfection by the same serotype, not only it does not protect against infection with other serotypes but it increases also the risk to develop a more severe disease upon secondary infection, a phenomenon attributed to non-neutralizing or sub-neutralizing antibodies and called Antibody-Dependent Enhancement (ADE) (Halstead S B et al. *Nature* 1977, 265(5596):739-741; Dejnirattisai W et al. *Science* 2010, 328(5979):745-748). In support of the ADE hypothesis, it was proposed that the low levels of serotype cross-reactive antibodies produced following a primary infection, can enhance the secondary infections through the formation of DENV-antibody complexes that bind to the Fcγ receptors (FcγR) on myeloid cells. This process leads to higher viral load and higher production of inflammatory mediators responsible of vascular permeability (Halstead S B et al. *Nature* 1977, 265(5596):739-741; Morens D M et al., *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 1994, 19(3):500-512; Halstead S B et al., *Advances in virus research* 2003, 60:421-467).

Mechanistically, ADE was shown to be critically dependent on the activation of FcγRIIa receptor expressed by monocytes, macrophages and dendritic cells (DCs) which produce high amounts of cytokines (TNF-α and IL-6) and chemokines (MIP-1a) upon stimulation (Wong K L et al., *PLoS ONE* 2012, 7(5):e36435; Boonnak K et al., *J Immunol* 2013, 190(11):5659-5665; Guilliams M et al., *Nat Rev Immunol* 2014, 14(2):94-108). The increased viral loads in ADE were also shown to result from the binding of immune complexes (between the virus and sub-neutralizing antibodies) to the leukocyte Ig-like receptor B1 (LILR-B1) on human primary monocytes, leading to the inhibition of the early antiviral responses mediated by the activated FcγRIIa (Chan K R et al., *Proc Natl Acad Sci USA* 2014, 111 (7):2722-2727).

Thus, depending on the nature of the DENV-specific antibody response, the adaptive immunity can induce either protection against infection or enhancement of infection and disease progression.

Like B cells, a pathogenic role of virus-specific T cells during secondary infection was also suggested. The hypothesis, called "original antigenic sin" postulated that, after a primary infection, cross-reactive memory T cells, with low avidity for the serotype of the secondary infection, dominate and mask the specific T cell response, leading to a less efficient killing of infected target cells (Mongkolsapaya J et al. *Nat Med* 2003, 9(7):921-927). These cross-reactive CD8+ T cells, stimulated upon a secondary infection with a different serotype, displayed also quantitative and qualitative differences in their response to the cross-reactive epitope or the altered peptide ligand (Bashyam H S et al., *J Immunol* 2006, 176(5):2817-2824).

However, in spite of these studies, the direct demonstration of a pathogenic role of DENV-specific T cells is still missing, and recent reports did not support a causative role for cross-reactive CD8+ T cells in the pathogenesis of dengue hemorrhagic fever during secondary infections. Indeed, a study in adults experiencing a secondary infection did not reveal any correlation between the magnitude and specificity of T-cell responses and clinical disease grade (Simmons C P et al., *J Virol* 2005, 79(9):5665-5675), and an important protective role for CD8+ T cells during primary DENV infection was also identified in a mouse model (Yauch L E et al. *J Immunol* 2009, 182(8):4865-4873). More strikingly, a detailed analysis of HLA-restricted T-cell responses in donors from hyperendemic area even reinforces the protective role of CD8+ T cells during DENV infection (Weiskopf D et al., *Proc Natl Acad Sci USA* 2013, 110(22): E2046-2053). It appears that, whereas serotype-specific responses are a hallmark of primary infection, there is a shift towards a response against conserved epitopes following secondary infection, without any difference in the avidity or functionality in CD8+ T cells among serotype-specific or conserved responses. In addition, a significant correlation was established between a weak T-cell response and disease susceptibility (Weiskopf D et al., *Proc Natl Acad Sci USA* 2013, 110(22):E2046-2053). Collectively, these studies highlight the beneficial effect of CD8+ T cells against disease progression in dengue virus infection.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1**. Immunogenicity of non-structural proteins NS3, NS4a, NS4b and NS5 of DENV1 and intra-serotype and inter-serotype amino acid sequence conservation of DENV. A. Weiskopf D et al., *Proc Natl Acad Sci USA* 2013, 110(22):E2046-2053; B. Rivino L et al., *J Virol* 2013, 87(5):2693-2706.

FIG. **2**. Amino acid sequence and secondary structure of NS DENV1 polyepitopic combined polyepitopic antigen (SEQ ID NO: 3). The following recitation of positions of amino acids in the sequence indicates the type of secondary structure in which the amino acid(s) is(are) involved in the corresponding full length protein as predicted for NS4B, or described in published crystallography studies for NS3 and NS5 (PDB ID 2VBC, *J Virol.* 2008 January; 82(1):173-183 and 2J7W, *J Virol.* 2007 May; 81(9):4753-65, respectively). In particular, alpha-helices are observed at the following segments of amino acid(s): 35-45; 57-66; 94-103; 123-138; 181-185; 189-198; 232-241; 247-254; 307-318; 342-360; 371-372; 374-375; 396-398; 406-419; 455-460; 468-473; 480-489; 500-517. Beta strands are observed at the following segments of amino acid(s): 20-23; 50-54; 72-74; 112-116; 142-146; 164-168; 276-277; 280-281; 283-285; 291-293; 366-370; 376-380; 436-442; 452-453. Bends are observed at the following segments of amino acid(s): 16; 55-56; 70; 80; 86-87; 89-93; 105; 111; 117; 122; 140; 148-49; 156-157; 161-162; 173-174; 178-179; 221; 243; 260-261; 287-288; 297-298; 305-306; 433-35; 449-450; 479; 492; 519-520. Turns are observed at the following segments of amino acid(s): 17-18; 27-29; 32-34; 46-47; 67-69; 77-78; 118-119; 139; 151-152; 186-187; 199-200; 204-205; 223-226; 230-231; 242; 255-257; 264-267; 278-279; 304; 319; 329-332; 420-423; 428-429; 474; 490-491; 518; 528-538. Moreover, 3/10 helices are observed at the following segments of amino acid(s): 213-218; 271-273; 301-303; 462-466 and 13 bridge is observed at the amino acids 188 and 300. Positions with conserved amino acids (found in more than 99.9% of a representative panel of 2033 sequences that include the 4 serotypes) are highlighted in dark grey.

FIG. **3**. Amino acid consensus sequences of DENV2-NS, DENV3-NS and DENV4-NS polyepitopes (SEQ ID NOs: 146, 147 and 148 respectively).

FIG. **4**. Alignment comparing the amino acid sequences of DENV1-NS, DENV2-NS, DENV3-NS and DENV4-NS consensus polyepitopes (SEQ ID NOs: 3, 146, 147 and 148 respectively).

FIG. **5**. Native nucleotide sequence of the polynucleotide encoding DENV1-NS polyepitope (SEQ ID NO: 1).

FIG. **6**. Optimised nucleotide sequence of the polynucleotide encoding DENV1-NS polyepitope (human codon optimized, measles optimized) (SEQ ID NO: 2).

FIG. **7**. Schematic representation of recombinant MV vectors expressing DENV antigens. The NS polyepitopic synthetic sequence was inserted into the ATU position 2 or 3 of MV vectors in combination or not with DENV EDIII tetrameric antigen. The MV genes are indicated as follows: nucleoprotein (N), phosphoprotein and V/C accessory proteins (PVC), matrix (M), fusion (F), hemagglutinin (H) and polymerase (L). T7 RNA polymerase promoter (T7), T7 RNA polymerase terminator (T7t), hepatitis delta virus ribozyme (a), hammerhead ribozyme (hh). In MVDVax9, the combined antigen inserted into the ATU position 2 is composed of a secreted DENV EDIII tetrameric protein fused to a secreted NS polyepitopic sequence with furin sites (having the amino acid sequence RRDKR as defined in SEQ ID NO: 152) inserted to separate the different components. In MVDVax11, on the contrary, the NS polyepitopic synthetic sequence is not secreted (no peptide leader sequence) and is fused in 3' to the exported DENV EDIII tetrameric protein (starting with peptide leader sequence).

FIG. **8**. Detection by western blot of the expression of DENV NS polyepitopic antigen (top) and DENV EDIII tetrameric antigen (bottom) in cell lysates of Vero cells infected by MV-DENV recombinant viruses or HEK293 cells transfected with pcDNA3-NS plasmid. DENV proteins were probed with specific Mabs.

FIG. **9**. DENV NS polyepitope peptides used for ELISPOT assays in CD46-IFNAR mice. Sequences 1-36 are 15-mer peptides overlapping of 5 aminoacids covering the entire DENV NS polyepitopic antigen. Peptides 37-41 were identified using prediction algorithms for their ability to bind H2-Db and H2-Kb T cell receptors expressed in CD46-IFNAR mice. These peptides have amino acid sequences as defined in SEQ ID NOs: 98-138.

FIG. **10**. ELISPOT quantification of T-cell responses in CD46-IFNAR mice immunized by MV-DENV vectors. Groups of six mice were immunized with MVDVax10, MVDVax8 or empty MV. ELISPOTS were quantified in splenocytes collected 7 days after a single immunization. Responses to DENV NS peptides, MV and concanavalin A as a positive control are shown.

FIG. **11**. ELISPOT quantification of T-cell responses in CD46-IFNAR mice immunized by MV-DENV vectors. The responses to different peptide pools or individual peptides covering the NS polyepitopic antigen are shown.

FIG. **12**. ELISPOT responses in CD46-IFNAR mice immunized by MV-DEBNV vectors cumulating the responses to individual peptides or pools.

FIG. **13**. Procedure for eliciting CD8+ T cell responses in H-2 Class I null/HLA Class I transgenic mice and quantification of IFN-γ response by ELISPOT assay.

FIG. **14**. Identification and HLA restriction of the immunogenic epitopes of the DENV1-NS polyepitopic construct (SEQ ID NO: 3).

FIG. **15**. Quantification of the T-cell responses in HLA-A2, A24, B7 and B35 transgenic mice by ELISPOT assay. Three independent experiments have been performed, in which a total of ten and four HLA-A*02:01 transgenic mice received the DENV1-NS polyepitopic construct (SEQ ID NO: 3) and the control plasmid, respectively, eight and four HLA-A*24:02 transgenic mice received the DENV1-NS polyepitopic construct and the control plasmid, respectively, five and four HLA-B*07:02 received the DENV1-NS polyepitopic construct and the control plasmid, respectively and five and three HLA-B*35:01 transgenic mice received the DENV1-NS polyepitopic construct and the control plasmid, respectively. All the animals were immunized by intradermic injection (100 μg DENV1-NS polyepitopic construct, or 100 μg pcDNA3.1 control plasmid) followed by in vivo electroporation. Two immunizations were performed at 3 week interval, and spleen cells were tested for IFN-γ secretion by ELISPOT 10 days after the second injection. Individual mice were tested in parallel with different peptides at 2 μg/ml and with concanavalin A (ConA) at 5 μg/ml, final concentration.

FIG. **16**. A) IFN-γ and B) Granzyme B (GrB) ELISPOT responses cumulating the responses to individual peptides. In these assays, the peptides used were: For HLA-A24 transgenic mice, peptides P17, P32 and P33 (having the amino acid sequences as defined in SEQ ID NO: 39, 33 and 47 respectively) were used as cognate, and peptide HBSP A2-2 (having the amino acid sequence TLCIPHVAV as defined in SEQ ID NO: 150) as control. For HLA-A2 transgenic mice, peptides P30, P53 and P56 were used as cognate (having the amino acid sequences as defined in SEQ ID NO: 18, 51 and 55 respectively), and peptide HBSP A2-2 as control. For HLA-B7 transgenic mice, peptides P15, P30 and P36 were used as cognate (having the amino acid sequences as defined in SEQ ID NO: 68, 18 and 21 respectively), and peptide Sv B7-3 (having the amino acid sequence SPFLPLLPI as defined in SEQ ID NO: 151) as control. For HLA-B35 transgenic mice, peptides P49, P50 and P51 were used as cognate (having the amino acid sequences as defined in SEQ ID NO: 28, 32 and 45 respectively), and peptide Sv B7-3 as control.

FIG. **17**. In vivo cytotoxic activity of T cells from animals immunized with the DENV1-NS polyepitopic construct (SEQ ID NO: 3) or the control plasmid. For HLA-A24 mice, high stained target cells were pulsed with a mix of P17, P32 and P33 cognate peptides (having the amino acid sequences as defined in SEQ ID NO: 39, 33 and 47 respectively), while low stained control cells were not pulsed. For HLA-A2 mice, high stained target cells were pulsed with a mix of P30, P53 and P56 cognate peptides (having the amino acid sequences as defined in SEQ ID NO: 18, 51 and 55 respectively), while low stained control cells were pulsed with the HBSP A2-2 control peptide. For HLA-B35 mice, high stained target cells were pulsed with a mix of P49, P50 and P51 cognate peptides (having the amino acid sequences as defined in SEQ ID NO: 28, 32 and 45 respectively), while low stained control cells were not pulsed.

FIG. **18** presents Table 1: DENV CD8 T+ cell epitopes having amino acid sequences as defined in SEQ ID NOs: 16-68. Amino acids differing from the described epitope are underlined; bCD8 T cell epitopes with positive score in the Elispot test are highlighted; cNT: not tested. References for HLA resctriction are as follows: (1) Rivino L et al., *J Virol* 2013, 87(5):2693-2706; (2) Simmons C P et al. *J Virol* 2005, 79(9):5665-5675; (3) lmrie A et al. *J Virol* 2007, 81(18): 10081-10091; (4) Boucherma R et al., *J Immunol* 2013, 191(2):583-593; (5) Weiskopf D et al., *Proc Natl Acad Sci USA* 2013, 110(22):E2046-2053; (6) Lund O et al., *PLoS ONE* 2011, 6(10):e26494; (7) Rivino L et al., *J Immunol* 2013, 191(8):4010-4019; (8) Nascimento E J et al., *PLoS neglected tropical diseases* 2013, 7(10):e2497; (9) Immune Epitope Database (IEDB); (10) Weiskopf D et al., *J Immunol* 2011, 187(8):4268-4279; (11) Yauch L E et al., *J Immunol* 2009, 182(8):4865-4873.

FIG. **19** presents Table 2. DENV CD4 T+ cell epitopes having amino acid sequences as defined in SEQ ID NOs: 69-97.

FIGS. **20**A to **20**D present Tables 3A-3D. Sequence conservation among the 4 DENV serotypes of epitopes of the NS polyepitope sequence identified in mice with 4 different HLA-restrictions. Predicted anchor residues are underlined and highlighted in grey. A) Peptides HLA-A*02:01; B) Peptides HLA-A*24:02; C) Peptides HLA-B*07:02;

DESCRIPTION OF THE INVENTION

The inventors have analyzed transcripts differentially expressed in peripheral blood mononuclear cells (PBMCs) from either asymptomatic or symptomatic infected donors from a cohort in Cambodia and observed a significant number of genes corresponding to CD8+ T cell activation overexpressed in asymptomatic individuals, in comparison with symptomatic donors, with Dengue Fever (DF) or Dengue Hemorrhagic Fever (DHF). A higher number of transcripts associated with TH17 and neutrophil activation were also observed in PBMC from these symptomatic patients with DHF and dengue shock syndrome (DSS), in agreement with the strong inflammatory response observed in severe dengue cases. Taken together, these observations strongly support an HLA-linked protective role for CD8+ T cells in anti-DENV immunity.

The inventors designed an antigen capable of inducing CD8+ T cell immunity to DENV. Most importantly, this antigen has a small size compared to the full length of the DENV genome, or to the full length of DENV NS proteins, so that it can be inserted in any vaccine vector, such as for example, a replicating viral vector derived from live-attenuated MV vaccine. Furthermore, this design aims at providing a DENV antigen enriched in highly antigenic epitopes, with the idea of limiting the exposure of the immune system to weakly immunogenic epitopes, and prevent the dispersion or dilution of the immune response. This antigen is composed of polyepitopic regions from NS proteins of DENV. Using compiled anti-DENV T-cell epitope distribution and strength (Simmons C P et al., *J Virol* 2005, 79(9):5665-5675; Yauch L E et al., *J Immunol* 2009, 182(8):4865-4873; Weiskopf D et al., *Proc Natl Acad Sci USA* 2013, 110(22): E2046-2053; Imrie A et al., *J Virol* 2007, 81(18):10081-10091; Lund O et al., *PLoS ONE* 2011, 6(10):e26494; Weiskopf D et al., *J Immunol* 2011, 187(8):4268-4279; Boucherma R et al., *J Immunol* 2013, 191(2):583-593; Nascimento E J et al., *PLoS neglected tropical diseases* 2013, 7(10):e2497; Rivino L et al., *J Virol* 2013, 87(5):2693-2706; Rivino L et al., *J Immunol* 2013, 191(8):4010-4019; Immune Epitope Database (IEDB)), the inventors selected four regions that are enriched in CD8 epitopes, for a total of 539 amino acids: two regions in NS3 (185 and 134 amino acids, respectively), one region in NS4b (86 amino acids) and one in NS5 (135 amino acids) (FIG. **1**). Borders of these 4 regions were chosen based on the secondary structure and amino acid sequence properties of the respective polypro-

teins, using crystallographic data for NS3 and NS5 (PDB ID 2VBC and 2J7W respectively), and using prediction tools such as JPRED (Cole C, Barber J D & Barton G J. *Nucleic Acids Res.* 2008. 35 (suppl. 2) W197-W201) or GOR IV (GOR secondary structure prediction method version IV, Methods in Enzymology 1996 R. F. Doolittle Ed., vol 266, 540-553, Gamier J, Gibrat J-F, Robson B) for NS4B, (FIG. **2**). Notably, the design carefully avoided the disruption of secondary structure elements such as α-helices or β-strands (FIG. **2**). A total of 2033 full-length dengue genome sequences (865 for serotype 1, 678 for serotype 2, 427 for serotype 3 and 63 for serotype 4) were aligned using MUSCLE 3.7 (Edgar R C, *Nucleic Acids Res* 2004, 32(5): 1792-1797), with manual adjustments according to the amino acid sequence. Sequence similarity was evaluated intra- and inter-serotypes at the nucleic and amino acid levels. Analysis of the concatenated regions of interest revealed strong intra-serotype conservation, and generally a higher degree of sequence identity compared to the genome as a whole, including for inter subtypes comparisons (FIGS. **1** and **2**). Based on the genetic diversity of the four serotypes of DENV, and with the idea that T cell epitopes are either conserved among different serotypes, or are serotype-specific with nevertheless the ability to induce cross-reactive CD8+ T-cell responses, a prototype consensus sequence based on epidemic strains of DENV1 was selected, the DENV1 NS T cell polyepitope (FIGS. **1** and **2**).

A serotype 1 consensus sequence was selected, as it presented the highest average genetic identity with the 4 serotypes (versus serotype 1: 99.48%; serotype 2: 83.48%; serotype 3: 89.39%; serotype 4: 76.96%).

Average genetic identity was estimated for each serotype as the percent sequence identity (ratio of identical positions over the total of aligned positions constituting the NS polyepitope) pairwise for each sequence of the serotype, and the average was reported. This percentage given corresponds only to the concatenation of the selected fragments of NS3, NS4B and NS5.

The invention thus relates to a chimeric polyepitope having less than 600 amino acid residues comprising or consisting of the following fragments of (a), (b) and (c) assembled in a fusion polypeptide wherein the fragments of (a), (b) and (c) are directly or indirectly fused in this order:

(a) two fragments of the non-structural (NS) NS3 protein of the dengue virus (DENV) serotype 1 (DENV1) comprising or consisting of two regions, wherein the first region has an amino acid sequence as defined in SEQ ID NO: 6, and the second region has an amino acid sequence as defined in SEQ ID NO: 9,

(b) a fragment of the NS4b protein of DENV1 having an amino acid sequence as defined in SEQ ID NO: 12,

(c) a fragment of the NS5 protein of DENV1 having an amino acid sequence as defined in SEQ ID NO: 15, or a polyepitope variant thereof, which (i) comprises or consists of the assembly in a fusion polypeptide, of DENV NS fragments, the sequences of which are obtained by alignment of the NS3 DENV1, NS4b DENV1, NS5 DENV1 fragments recited in (a), (b) and (c) with the respective NS3, NS4b and NS5 sequences of the NS proteins of a virus of the DENV2, DENV3 or DENV4 serotype or (ii) consists of a chimeric polyepitope having an amino acid sequence which has more than 75% identity, in particular more than 80% or more than 85% or more than 90% identity with the sequence of the fusion polypeptide consisting of fused fragments (a), (b) and (c) (from which it derives by mutation of amino acid residues), over its whole length.

In a particular embodiment, the present invention relates to a chimeric polyepitope having a size of less than 600 amino acid residues, in particular consisting of a strand of 539 amino acid residues and comprising or consisting of the fusion of fragments named (a), (b) and (c) hereafter and obtained from or representative of several non-structural (NS) proteins of any DENV genome, namely fragments consisting of:

(a) the NS3 protein consisting of amino acids 1645 to 1829 and 1959 to 2092 in the polyprotein sequence of DENV1 (Genbank accession number NP_059433.1), or amino acids 1645 to 1828 and 1958 to 2091 in the polyprotein sequence of DENV2 (Genbank accession number NP_056776.2), or amino acids 1643 to 1827 and 1957 to 2090 in the polyprotein sequence of DENV3 (Genbank accession number YP_001621843.1), or amino acids 1644 to 1827 and 1957 to 2090 in the polyprotein sequence of DENV4 (Genbank accession number NP_073286.1),

(b) the NS4b protein consisting of amino acids 2262 to 2347 in the polyprotein sequence of DENV1 (Genbank accession number NP_059433.1), or amino acids 2260 to 2345 in the polyprotein sequence of DENV2 (Genbank accession number NP_056776.2), or amino acids 2260 to 2344 in the polyprotein sequence of DENV3 (Genbank accession number YP_001621843.1), or amino acids 2259 to 2341 in the polyprotein sequence of DENV4 (Genbank accession number NP_073286.1), and

(c) the NS5 protein consisting of amino acids 2766 to 2899 in the polyprotein sequence of DENV1 (Genbank accession number NP_059433.1), or amino acids 2765 to 2898 in the polyprotein sequence of DENV2 (Genbank accession number NP_056776.2), or amino acids 2763 to 2896 in the polyprotein sequence of DENV3 (Genbank accession number YP_001621843.1), or amino acids 2761 to 2894 in the polyprotein sequence of DENV4 (Genbank accession number NP_073286.1),

wherein each fragment (a), (b) and (c) comprises a plurality of epitopes suitable for the elicitation of an immune response, especially an immune T-cell response against all DENV serotypes, said polyepitope resulting from direct or indirect fusion of the plurality of said fragments, in particular said fragments originating from a unique dengue virus serotype.

In a particular embodiment, the present invention relates to a chimeric polyepitope having a size of 539 amino acids, and comprising or consisting of the fusion of fragments named (a), (b) and (c) hereafter and obtained from or representative of several non-structural (NS) proteins of any DENV genome, namely fragments consisting of:

(a) the NS3 protein encoded by nucleotides 5027 to 5581 and 5969 to 6370 in the nucleotide sequence of DENV1 (Genbank accession number NC_001477.1), or nucleotides 5026 to 5580 and 5968 to 6369 in the nucleotide sequence of DENV2 (Genbank accession number NC_001474.2), or nucleotides 5021 to 5575 and 5963 to 6364 in the nucleotide sequence of DENV 3 (Genbank accession number NC_001475.2), or nucleotides 5028 to 5582 and 5970 to 6371 in the nucleotide sequence of DENV 4 (Genbank accession number NC_002640.1),

(b) the NS4b protein encoded by nucleotides 6878 to 7135 in the nucleotide sequence of DENV1 (Genbank accession number NC_001477.1), or nucleotides 6874 to 7131 in the nucleotide sequence of DENV2 (Genbank accession number NC_001474.2), or nucleotides 6872 to 7126 in the nucleotide sequence of DENV 3 (Genbank accession number

NC_001475.2), or nucleotides 6876 to 7124 in the nucleotide sequence of DENV 4 (Genbank accession number NC_002640.1), and

(c) the NS5 protein encoded by nucleotides 8390 to 8791 in the nucleotide sequence of DENV1 (Genbank accession number NC_001477.1), or nucleotides 8389 to 8790 in the nucleotide sequence of DENV2 (Genbank accession number NC_001474.2), or nucleotides 8381 to 8782 in the nucleotide sequence of DENV 3 (Genbank accession number NC_001475.2), or nucleotides 8382 to 8783 in the nucleotide sequence of DENV 4 (Genbank accession number NC_002640.1),

wherein each translated fragment (a), (b) and (c) comprises a plurality of epitopes suitable for the elicitation of an immune response, especially an immune T-cell response against all DENV serotypes, said polyepitope resulting from direct or indirect fusion of the plurality of said fragments in particular said fragments originating from a unique dengue virus serotype.

As defined herein, the term "polyepitope" refers to a polypeptide with advantageously at least 3 and in particular at least 5 and preferably more than 10 or more than 13 epitopes identified in DENV1 NS3, NS4b and NS5 proteins, in particular T-cell epitopes of DENV1 NS3, NS4b or NS5 consensus sequence provided in FIG. **1**. Epitopes within the present invention are, either linear or conformational, preferably linear, and are any peptide or polypeptide involved in the induction of a cell-mediated immune response, especially a T cell immune response against a DENV and in particular against anyone of DENV1, DENV2, DENV3, DENV4 or against multiple, in particular all DENV serotypes. Accordingly, epitopes described herein include those which are processed by APC (Antigen Presenting Cells) in a host, especially T epitopes recognized in association with class I MHC (Major Histocompatibility Complex) molecules, such as epitopes which target cells are CD8+T lymphocytes or T epitopes recognized in association with class II MHC molecules, such as those which target cells are CD4+T lymphocytes.

The term "chimeric polyepitope" means any polyepitopic polypeptide comprising sub-portions of different DENV NS proteins selected among NS3, NS4b and NS5 proteins, for example a polyepitope deriving from a first DENV NS protein and a polyepitope deriving from a second DENV NS protein as defined herein. A polyepitope is also considered to be a chimeric polyepitope if it includes sub-portions deriving from different polyepitopes from the same DENV NS protein, or even from the same polyepitopes from different DENV NS proteins. The chimeric polyepitope of the invention includes the polyepitope variant. Accordingly each definition or embodiment disclosed herein applies to the variant polyepitope unless it is technically irrelevant.

In a particular embodiment of the invention, the chimeric polyepitope comprises human leukocyte antigen (HLA)-restricted epitopes. The expression "HLA-restricted" refers to the capacity for a particular epitope to have an affinity for this type of HLA molecule. The HLA molecules used in the invention encompass either class I molecules (designated HLA-A, B or C) or class II molecules (designated DP, DQ or DR).

In another particular embodiment of the invention, the chimeric polyepitope elicits a human leukocyte antigen (HLA)-restricted $CD8^+$ and/or $CD4^+$ T cell response against DENV1, DENV2, DENV3 and DENV4. A non-exhaustive list of DENV CD8 T cell epitopes is provided in Table 1.

In another particular embodiment of the invention, the chimeric polyepitope elicits a human leukocyte antigen (HLA)-restricted $CD4^+$ T cell response against DENV1, DENV2, DENV3 and DENV4. A non-exhaustive list of DENV CD4 T cell epitopes is provided in Table 2.

In a particular embodiment, the NS chimeric polyepitope sequence has been shown to elicit antigenic responses in mice with HLA restriction such as HLA-A*02:01, HLA-A*24:02, HLA-B*07:02 or HLA-B*35:01.

In a particular embodiment, the present invention relates to a chimeric polyepitope, whose size is 539 amino acids, comprising or consisting of:

(a) two fragments of the non-structural (NS) NS3 protein of the dengue virus (DENV) serotype 1 (DENV1), having amino acid sequences as defined in SEQ ID NO: 6, SEQ ID NO: 9, respectively,

(b) a fragment of the NS4b protein of DENV1 comprising amino acid sequences as defined in SEQ ID NO: 12,

(c) a fragment of the NS5 protein of DENV1 comprising amino acid sequences as defined in SEQ ID NO: 15, and wherein each NS fragment (a), (b) and (c) is fused directly or indirectly with another NS fragment (a), (b) and (c) in the polyepitope, preferably in this order.

Nucleotide sequences of the polyprotein of DENV1, DENV2, DENV3 and DENV4 can be accessed from the Genbank accession numbers NP_059433.1, NP_056776.2, YP_001621843.1 and NP_073286.1 respectively.

Amino acid sequences of DENV2-NS, DENV3-NS and DENV4-NS polyepitopes of SEQ ID NO: 146, 147 and 148 respectively which are variant polyepitopes of the invention are disclosed in FIG. **3**. The inventors have carried out an alignment showing conserved amino acid residues in sequences of DENV1-NS, DENV2-NS, DENV3-NS and DENV4-NS polyepitopes (FIG. **4**).

In a preferred embodiment of the invention, the chimeric polyepitope comprises at least the P30, P451, P36, P453, P49, P50, P32, P17, P21, P51, P33, P56 and P15 epitopes disclosed herein. In particular, the P30, P451 and P56 epitopes are restricted by HLA-A*02:01, the P17, P32 and P33 epitopes are restricted by HLA-A*24:02, the P15, P30 and P36 epitopes are restricted by HLA-B*07:02 and the P21, P49, P50, P51 and P453 epitopes are restricted by HLA-B*35:01. The chimeric polyepitope is expected to contain a number of additional epitopes at least equal to the number of existing HLA, with examples provided in Tables 1 and 2.

The epitopes of the invention can have amino acid sequences that are distinct or that differ by one or more amino acids in the consensus NS determined for DENV1 within the frame of the invention. Alternatively or in addition, two epitopes of the polyepitope of the invention can have overlapping sequences in one NS fragment, and accordingly share some amino acids.

Chimeric polyepitopes of the invention can be synthesized chemically, or produced either in vitro (cell free system) or in vivo after expression of the nucleic acid molecule encoding the polyepitope in a cell system.

As defined herein, the term "fragment" refers to parts or portions of NS proteins (i.e. NS3, NS4b or NS5 protein), in particular portions having from 86 to 185 amino acids. Any sequence or combination of sequences of any dengue virus isolate corresponding to the fragments of the invention (as delimited by the positions in the NS proteins as identified using nucleotide and amino acid numbering on DENV1 reference sequence deposited in Genbank (NP_059433.1) or as disclosed with respect to its SEQ ID NO. is shorter in length than the NS protein from which it originates.

According to a particular embodiment of the invention, one NS fragment is fused "directly" with another NS frag-

ment, i.e. the 3' end of the NS fragment is directly linked to the 5' end of the second fragment (and so on), corresponding to a chimeric polyepitope composed of consecutive NS fragments from the same and/or from different NS proteins chosen among NS3, NS4b and NS5, in particular originating from NS consensus sequence of DENV1. According to an alternative embodiment, the fusion of the fragments is "indirect" and accordingly involves the presence of non-NS amino acid residues segment(s), i.e., amino acid residues segments which do not read on the NS protein providing the sequence of the considered fragment.

As defined herein, the term "region" refers to contiguous amino acid strand of a NS protein as defined herein, having at least 86 amino acids. A fragment of a NS protein may comprise or consist of a plurality of regions as for the NS3 fragment.

The term "percentage identity" between two compared nucleotidic sequences or respectively two amino acid sequences as used in the present invention means a percentage of identical nucleotides or amino acids between the two sequences to be compared, obtained after best alignment, that percentage being purely statistical and the differences between the two sequences being randomly distributed and over their entire length. The term "best alignment" or "optimum alignment" means the alignment at which the percentage of identity is the highest. Sequence comparisons between two nucleic acid or amino acid sequences are traditionally carried out by comparing these sequences after having aligned them in an optimum manner, said comparison being carried out using comparison segments or windows to identify and compare local regions with sequence similarity. The optimum sequence alignment for comparison may be carried out manually or using a Smith and Waterman (1981) local homology algorithm, using the Neddleman and Wunsch (1970) local homology algorithm, using the Pearson and Lipman (1988) sequence similarity search method, or using software employing these algorithms (GAP, BESTFIT, BLAST P, BLAST N, FASTA and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr, Madison, Wis.). To obtain an optimal alignment, the BLAST program may be used, with the BLOSUM 62 matrix. It is also possible to use PAM or PAM250 matrices. A total of 2033 full-length dengue genome sequences (865 for serotype 1, 678 for serotype 2, 427 for serotype 3 and 63 for serotype 4) were aligned using MUSCLE 3.7 (Edgar R C, *Nucleic Acids Res* 2004, 32(5): 1792-1797), with manual adjustments according to the amino acid sequence.

The percentage identity between two nucleic acid or two amino acid sequences is determined by comparing these two sequences aligned in an optimum manner. The percentage identity is calculated by determining the number of identical positions for which the nucleotide or amino acid residue is identical between the two sequences, dividing this number of identical positions by the total number of compared positions and multiplying the result obtained by 100 to obtain the percentage identity between these two sequences.

In a particular embodiment of the invention, the first region of NS3 of DENV1 has an amino acid sequence as defined in SEQ ID NO: 6, the second region of NS3 of DENV1 has an amino acid sequence as defined in SEQ ID NO: 9, the NS4b fragment of DENV1 has an amino acid sequence as defined in SEQ ID NO: 12 and the NS5 fragment of DENV1 has an amino acid sequence as defined in SEQ ID NO: 15.

In another particular embodiment of the invention, the native and optimised sequences of the polynucleotide encoding the first region of NS3 of DENV1 are as defined in SEQ ID NOs: 4 and 5 respectively, the native and optimised sequences of the polynucleotide encoding the second region of NS3 of DENV1 are as defined in SEQ ID NOs: 7 and 8 respectively, the native and optimised sequences of the polynucleotide encoding the NS4b fragment of DENV1 are as defined in SEQ ID NOs: 10 and 11 respectively, and the native and optimised sequences of the polynucleotide encoding the NS5 fragment of DENV1 are as defined in SEQ ID NOs: 13 and 14 respectively.

The term "variants" encompasses the assembly of the other fragments of the NS3, NS4b and NS5 proteins of a virus of the DENV serotype 2, 3 or 4, as disclosed herein.

In a preferred embodiment of the invention, the chimeric polyepitope comprises or consists of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 146, 147 and 148.

The present invention also relates to an association of the chimeric polyepitope of the invention, with a distinct immunogenic polypeptide hereafter designated as tetravalent EDIII/ectoM. In a particular embodiment of the invention, said distinct immunogenic polypeptide (tetravalent EDIII/ectoM) consists of chimeric DENV antigens composed of the fusion of the EOM polypeptides representative of the four DENV serotypes, fused to ectoM of DENV1, and has an amino acid sequence as disclosed in SEQ ID NO: 145, and is encoded by the polynucleotide having SEQ ID NO: 144.

Said association of polypeptides may be achieved as a result of expression of the polynucleotides encoding each of said chimeric polyepitope and distinct immunogenic polypeptide, from a vector as disclosed herein. Alternatively, said association may result from an amino acid construct encompassing said chimeric polyepitope and distinct immunogenic polypeptide.

The present invention also relates to viral particles, in particular recombinant measles virus (MV) particles expressing a chimeric polypeptide of the invention or said chimeric polypeptide in association with the tetravalent EDIII/ectoM polypeptide.

The present invention also relates to a vector comprising or consisting of recombinant measles virus (MV) particles expressing the chimeric polyepitope of the invention and optionally the tetravalent EDIII/ectoM immunogenic polypeptide.

The thus produced recombinant viral particles, in particular measles virus particles have proved to enhance the immune response elicited by the DENV antigens when used alone, in particular by impacting the immunogenic T-cell response elicited following administration of the particles to a host in need thereof.

In order to prepare the viral particles, in particular MV particles expressing the chimeric polyepitope of the invention in association with the so-called tetravalent EDIII/ectoM polypeptide as disclosed herein, the polynucleotide(s) encoding said polyepitope and polypeptide are recombined into a polynucleotide encompassing the genome of the virus, especially the genome of the measles virus.

According to a preferred embodiment of the invention, the recombinant MV genome is provided as a cDNA encoding the full-length RNA genome of a live-attenuated Schwarz or Moraten virus.

A live-attenuated MV strain refers to a strain which has been serially passaged on selected cells and, preferably, adapted to other cells such as primary cells with an IFN a/13 response, i.e. CEF cells, to produce seed strains suitable for the preparation of vaccine strains, harboring a stable genome

which would not allow reversion to pathogenicity nor integration into host chromosomes, in particular human host chromosomes. In a particular embodiment of the invention, a live-attenuated MV is one which has been selected on primary cells such as CEF cells.

As defined herein, the expression "live-attenuated Schwarz or Moraten virus" designates a Schwarz or Moraten virus originating from a strain that is avirulent or less virulent than a determined parent strain in the same host, especially in human, while maintaining infectious properties and immunogenicity and possibly adjuvancy when administered in a host, especially in human. In particular, the Schwarz strain or the Moraten strain is from the Rouvax® vaccine (Aventis). It has been demonstrated that the Schwarz strain has a perfect identity of sequence with the Moraten strain (Parks, C. L. et al., 2001, *J Virol,* 75(2): 910-920; Schwarz, A. J., 1962, *Am J Dis Child,* 103, 386-389). The Schwarz/Moraten strains are currently widely-used since they induce long-term cell and humoral immune responses and present an important genetic stability since no reversion to a pathogenic form has ever been observed (Hilleman, M., 2002, *Vaccine,* 20:651-665).

The measles virus genome is obtained as a result of preparation of a cDNA molecule encoding the full-length MV genome as disclosed in the art especially in WO 2004/001051 and WO 2004/000876. Said cDNA molecule has been included as an insert in a plasmid designated pTM-MVSchw deposited on Jun. 12, 2002 with the CNCM under No. 1-2889 (Institut Pasteur-Paris-France). The sequence of the MV cDNA encoding the genome is provided in the figures illustrating the constructs prepared with the chimeric polyepitope of the invention and the distinct so-called tetravalent EDIII/ectoM polypeptide. The position of the MV sequences is disclosed in said figures.

In order to express the chimeric polyepitope of the invention and optionally the distinct so-called tetravalent EDIII/ectoM polypeptide, said cDNA molecule encoding the full-length MV genome is recombined with a DNA molecule encoding the chimeric polyepitope of the invention and optionally in a DNA molecule encoding the so-called tetravalent EDIII/ectoM polypeptide as disclosed herein, using methods and protocols well-known from the person skilled in the art. The DNA molecules encoding said polypeptides are prepared according to known techniques, by the skilled person.

In a particular embodiment, a DNA molecule corresponding to the chimeric polyepitope of the invention can be generated by chemical synthesis. Preferably, this sequence is codon-optimized for expression in mammalian cells and preferably its length fulfills the "rule of six" which stipulates that the total number of nucleotides is a multiple of 6, which rules is known to impact the proper expression of the MV proteins from the MV genome (Calain, P. et al. *J Virol.,* 1993, 67:4822-4830).

In a particular embodiment, all nucleic acid constructs inserted in the cDNA encoding the full-length MV genome, in particular coding sequences for the chimeric polyepitope and for the so-called tetravalent EDIII/ectoM polypeptide have a number of nucleotides which is a multiple of six.

The present invention thus relates to an isolated or purified polynucleotide encoding the chimeric polyepitope of the invention, and having preferably a total number of nucleotides which complies with the rule of six. This polynucleotide is in particular a DNA or a cDNA. In a particular embodiment, MV editing- and polyadenylation-like sequences of the sequence encoding the NS fragments of the polynucleotide of the invention are mutated (Lamb, R. A. et al. In Fields Virology, 4th edition, 1305-1340; Schneider, H. et al. *Virology,* 1997, 227: 314-322). In addition, to allow its future cloning into a plasmid such as pUC into a mammalian expression plasmid such as pcDNA3, or into MV vector, the DNA encoding the chimeric polyepitope of the invention was flanked by sequences of restriction sites such as BgIII, ApaI, BsiWI and BssHII.

The invention accordingly concerns in particular the native and codon optimized nucleotide sequences encoding the chimeric polyepitope of DENV1 which are the sequences disclosed as SEQ ID NO: 1 and SEQ ID NO: 2 respectively (FIGS. **5** and **6**). Amino acid sequence of the chimeric polyepitope of DENV1 is the sequence disclosed as SEQ ID NO: 3.

The present invention also relates to an isolated or purified polynucleotide encoding the chimeric polyepitope of the invention, in a nucleic acid construct further comprising a polynucleotide encoding tetravalent DENV antigens composed of the fusion of the EDIII polypeptides of the four serotypes, fused to ectoM of DENV1, wherein the polynucleotide obtained has preferably a total number of nucleotides which complies with the rule of six. In a particular embodiment, this polynucleotide has the sequence of SEQ ID NO: 144. Such a construct may in particular comprise the polynucleotide encoding tetravalent DENV antigens composed of the fusion of the EDIII polypeptides of the four serotypes, fused to ectoM of DENV1 upstream from the polynucleotide encoding the chimeric polyepitope of the invention.

The invention also relates to a nucleic acid molecule comprising the herein disclosed polynucleotide encoding the chimeric polyepitope of the invention and optionally comprising the polynucleotide encoding tetravalent DENV antigens composed of the fusion of the EDIII polypeptides of the four serotypes, fused to ectoM of DENV1 recombined with the cDNA molecule encoding the full-length MV genome.

As defined herein, the term "isolated or purified" means molecules which have been altered by man from their native state, i.e. if the molecules exist in nature, they have been changed and/or withdrawn from their initial environment. As an example, a polynucleotide naturally present and found in the biological environment of a living organism which naturally expresses it is not "isolated" in this context. However, the same polynucleotide when separated from its natural environment and/or obtained by cloning, amplification and/or chemical synthesis is considered in the present invention to be "isolated". Further, a polynucleotide which is introduced into an organism by transformation, gene manipulation or any other recombination method is "isolated" even if it is present in said organism.

The term "encoding" used in the present application defines the ability of the nucleic acid molecules to be transcribed and where appropriate translated for product expression into selected cells or cell lines, when said molecule is placed under expression control sequences including promoter for transcription. Accordingly a "polynucleotide encoding" according to the invention is either limited to the nucleic acid having the sequence translated into the amino acid sequence or alternatively when specified comprises also the expression control sequences.

The invention also relates to a vector. As used herein, the term "vector" refers to a polynucleotide construct designed for transduction/transfection of one or more cell types. Vectors may be, for example, "cloning vectors" which are designed for isolation, propagation and replication of inserted polynucleotides (designated as the insert), "expression vectors" which are designed for expression of a poly-

nucleotide molecule especially for expression of the insert in a host cell, or a "viral vector" which is designed to result in the production of recombinant virus particles or virus-like particles, or "shuttle vectors", which comprise the attributes of more than one type of vector.

A number of vectors suitable for transduction or for transfection of cells, in particular for stable transfection of cells and bacteria are available to the public (e.g. plasmids, viruses), as are methods for constructing such cell lines. It will be understood that the present invention encompasses any type of vector comprising any of the polynucleotides of the invention.

The present invention accordingly relates to a vector, in particular an expression vector, which may be a plasmid comprising as polynucleotide insert(s), one or a plurality of the nucleic acid molecules defined herein. In a particular embodiment, the plasmid comprises as an insert a polynucleotide encoding the chimeric polyepitope of the invention as defined herein and optionally comprises the polynucleotide encoding tetravalent DENV antigens composed of the fusion of the EDIII polypeptides of the four serotypes, fused to ectoM of DENV1.

In a particular embodiment, the present invention concerns a plasmid (designated measles genome vector) comprising (i) a cDNA encoding the full-length RNA genome of a measles virus (MV), which cDNA is recombined with (ii) a polynucleotide according to the invention encoding the chimeric polyepitope of the invention as defined herein and optionally (iii) a polynucleotide encoding tetravalent DENV antigens composed of the fusion of the EDIII polypeptides of the four serotypes, fused to ectoM of DENV1 as defined herein. In a particular embodiment when the sequences of (i), (ii) and optionally (iii) are present in the MV genome vector, they comply together with the rule of six.

In a particular embodiment said polynucleotide(s) is(are) located as separate insert(s) between the P and M genes of the MV genome, or between the H and L genes of the MV genome. Optionally said insert(s) is(are) located in an Additional Transcription Unit (ATU) such as the ATU having the sequence of ATU 2 or ATU3 illustrated in the construct MDVVax6. The location of the ATU within the cDNA derived from the antigenomic RNA of MV can vary along said cDNA.

In a particular embodiment, the present invention concerns a recombinant measles virus (MV) genome vector, which is a plasmid comprising (i) a cDNA encoding the full-length RNA genome of a MV virus and (ii) the polynucleotide encoding the chimeric polyepitope according to the invention, said polynucleotide being located as an insert between the P and M genes of the MV genome or between the H and L genes of the MV genome, optionally in an Additional Transcription Unit (ATU), wherein the sequences of (i) and (ii) when recombined in the plasmid together comply with the rule of six.

The present invention also concerns a recombinant MV genome vector, which is a plasmid comprising (a) a cDNA encoding the full-length RNA genome of a MV virus, (b) a polynucleotide encoding tetravalent DENV antigens composed of the fusion of the envelope domain III (EDIII) polypeptides of the four DENV serotypes, fused to the ectodomain of the membrane protein (ectoM) of DENV1, in particular DENV antigens having the sequence of SEQ ID NO: 145 and (c) the polynucleotide according to the invention, wherein:

the polynucleotide (b) is located as an insert between the P and M genes of the MV genome and the polynucleotide (c) is located as an insert between the H and L genes of the MV genome, or

the polynucleotide (b) is located as an insert between the P and M genes of the MV genome and the polynucleotide (c) is located as an insert between the P and M genes of the MV genome, or

the polynucleotide (b) is located as an insert between the H and L genes of the MV genome and the polynucleotide (c) is located as an insert between the P and M genes of the MV genome and wherein the sequences of (a), (b) and (c) when recombined in the plasmid together comply with the rule of six.

In a particular embodiment, when the sequences of (a), (b) and (c) are recombined in a plasmid they together comply with the rules of six.

The nucleotide sequences of particular vectors of the invention comprising both polynucleotides are the sequences disclosed as SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143 and SEQ ID NO: 149.

The present invention also relates to a host cell genetically transformed with the polynucleotide encoding the chimeric polyepitope of the invention and optionally with the polynucleotide encoding the tetravalent EDIII/ectoM according to the invention, in particular a polynucleotide encoding tetravalent DENV antigens composed of the fusion of the envelope domain III (EDIII) polypeptides of the four DENV serotypes, fused to the ectodomain of the membrane protein (ectoM) of DENV1. A particular host cell may thus be genetically transformed with a vector of the invention, in particular with a recombinant MV genome vector of the invention.

The host cell of the invention is transfected with a genome vector of the invention, by methods well known to the man skilled in the art, i.e. by chemical transfection (calcium phospate, lipofectamine), lipid-based techniques (liposome), electroporation, photoporation, use of viral vectors . . . .

In a particular embodiment, a cell is transformed or transduced with a polynucleotide of the invention, in a way enabling integration of the polynucleotide in the cell genome either by a recombination with the homologous cellular sequence or by insertion in the cellular genome. The transfection, infection or transduction can occur ex vivo, i.e. in an artificial environment outside the living organism.

As used herein, the terms "transfected", "transformed" or infected" refer to a cell comprising a vector of the invention (transient expression), whereas the term "genetically transformed" refers to a cell whose genome has been definitively modified by a polynucleotide of the invention (permanent expression).

Said transitory or stably transformed cells can be any prokaryotic (bacteria) or eukaryotic (yeast, insect or animal including mammal especially human) cells. In an embodiment, cells are non-human cells. In a particular embodiment, cells of the invention are isolated human cells, "isolated" meaning outside of their natural environment.

In a particular embodiment of the invention, the cell is HEK-293-T7-MV cell line.

More preferably, an infectious recombinant MV genome vector suitable to carry out the invention is produced using a cDNA of MV Schwarz strain cloned into the plasmid pTM-MVSchw, deposited by Institut Pasteur at the CNCM (Paris, France) under number 1-2889 on Jun. 12, 2002, the sequence of which is described by Combredet (Combredet, C. et al., 2003, *J Virol,* 77(21): 11546-11554), and also disclosed in WO2004/000876. The plasmid pTM-MVSchw has been obtained from a Bluescript plasmid, and comprises

the polynucleotide coding for the full-length MV (+) RNA strand of the Schwarz strain placed under the control of the promoter of the T7 RNA polymerase, and has 18967 nucleotides. cDNAs from other MV strains may be similarly obtained starting from the nucleic acid purified from viral particles of live-attenuated MV. Accordingly a recombinant MV genome vector of the invention is pTM-MVDVax6 as illustrated by SEQ ID NO: 139, pTM-MVDVax7 as illustrated by SEQ ID NO: 140, pTM-MVDVax8 as illustrated by SEQ ID NO: 141, pTM-MVDVax9 as illustrated by SEQ ID NO: 142, pTM-MVDVax10 as illustrated by SEQ ID NO: 143 or pTM-MVDVax11 as illustrated by SEQ ID NO: 149.

The plasmid comprising the recombinant MV genome thus defined (genome vectors) are suitable for use in a rescue system for the preparation of recombinant measles virus particles.

Rescue of recombinant MV viruses can be performed as previously described (Combredet et al., *J Virol.,* 2003, 77(21): 11546-11554), in particular using stable HEK293-T7-MV helper cells (WO2004/000876).

In order for the rescue of recombinant MV particles to be achieved and enable the assembly of recombinant MV particles of the invention, helper cells (host cells) are used which express an RNA polymerase such as the T7 RNA polymerase and the N, P and L proteins of MV and which are genetically transformed with a MV genome vector according to the invention. The expression of the MV proteins by the helper cell may be obtained by genetically transforming the helper cell with additional, vectors such as transcomplementation plasmids, expressing an RNA polymerase such as the T7 RNA polymerase and the N, P and L proteins of MV.

In a particular embodiment of the invention, the helper cell line is the 293-T7-NP cell line deposited with the Collection Nationale de Cultures de Micro-organismes (CNCM) on Jun. 14, 2006, under number 1-3618 or the 293-nIsT7-NP MV cell line deposited with the CNCM on Aug. 4, 2006, under number 1-3662.

The present invention also relates to recombinant MV particles, which are rescued from a helper cell line expressing the T7 RNA polymerase and the N, P and L proteins of MV, and which further expresses a nucleic acid encoding a vector of the invention or a nucleic acid encoding a recombinant MV genome vector of the invention.

In a further aspect, the present invention relates to an immunogenic composition comprising (a) DENV antigens composed of the fusion of the EDIII polypeptides of the four DENV serotypes, fused to ectoM of DENV1, in particular DENV antigens having the sequence of SEQ ID NO: 145 and (b) the chimeric polyepitope according to the invention, which optionally does not comprise an accessory adjuvant.

The present invention also relates to an immunogenic composition comprising recombinant MV particles according to the invention, which composition optionally does not comprise an accessory adjuvant. Interestingly, the recombinant MV particles of the invention are capable of eliciting a humoral and/or a cellular immune response(s) against the dengue virus infection or against both MV and the dengue virus infection, in a host upon administration. In a particular embodiment, the immunogenic composition of the invention elicits an immune response, in particular a T-cell immune response against the DENV1, DENV2, DENV3 and DENV4 and accordingly may elicit a protective response against infection by any virus of these DENV 1 to 4 serotypes.

According to a particular embodiment of the invention, the immunogenic composition is formulated for an administration through parenteral route such as subcutaneous (s.c.), intradermal (i.d.), intramuscular (i.m.), intraperitoneal (i.p.) or intravenous (i.v.) injection.

According to another particular embodiment of the invention, the immunogenic composition is administered in one or multiple administration dose(s), in particular in a prime-boost administration regime.

In a particular embodiment, the immunogenic composition does not comprise an accessory adjuvant.

The quantity to be administered (dosage) depends on the subject to be treated, including the condition of the patient, the state of the individual's immune system, the route of administration and the size of the host. Suitable dosages range from 10^3 TCID50 to 10^7 TCID50 and can be modified by one skilled in the art, depending on circumstances.

The present invention also relates to a vaccine composition comprising (a) DENV antigens composed of the fusion of the EDIII polypeptides of the four DENV serotypes, fused to ectoM of DENV1, and (b) the chimeric polyepitope according to the invention, which optionally does not comprise an accessory adjuvant.

The present invention also relates to a vaccine composition comprising recombinant MV particles according to the invention, which optionally does not comprise an accessory adjuvant.

The present invention also relates to a method to prevent and/or treat a dengue virus infection in a human subject comprising administering a pharmaceutically effective quantity of recombinant MV particles according to the invention or an immunogenic composition according to the invention, wherein said particles or composition are in admixture with a pharmaceutically acceptable vehicle; and/or an adjuvant.

As used herein, the term "to prevent" refers to a method by which a dengue virus infection is obstructed or delayed.

As used herein, the term "to treat" refers to a method by which the symptoms of a dengue virus infection are either alleviated, i.e. decrease of the dengue virus infection in the host or improvement of the clinical condition of the patient, or completely eliminated.

As defined herein, a pharmaceutically acceptable vehicle encompasses any substance that enables the formulation of the chimeric polyepitope, the polynucleotide, the vector, in particular the recombinant MV genome vector according to the invention within a composition. A vehicle is any substance or combination of substances physiologically acceptable i.e., appropriate for its use in a composition in contact with a host, especially a human, and thus non-toxic. Examples of such vehicles are phosphate buffered saline solutions, distilled water, emulsions such as oil/water emulsions, various types of wetting agents sterile solutions and the like.

As defined herein, an adjuvant includes, for example, liposomes, oily phases, such as Freund type adjuvants, generally used in the form of an emulsion with an aqueous phase or can comprise water-insoluble inorganic salts, such as aluminium hydroxide, zinc sulphate, colloidal iron hydroxide, calcium phosphate or calcium chloride.

The present invention also relates to a method to produce recombinant MV particles for the preparation of an anti-dengue virus vaccine, comprising or consisting of:

a) transfecting a recombinant MV genome vector according to the invention, in a helper cell line which expresses the T7 RNA polymerase and the N, P and L proteins of MV;

b) transferring said helper cell line onto cells competent to sustain the replication and production of recombinant MV particles expressing a chimeric polyepitope according to the invention and optionally a polypeptide comprising a tetrava-

lent DENV antigen composed of the fusion of the EDIII polypeptides of the four serotypes, fused to ectoM of DENV1, in particular DENV antigens having the sequence of SEQ ID NO: 145; and

c) recovering the recombinant MV particles produced in step b).

In a preferred embodiment of the invention, the competent cells in step b) are Vero (African green monkey kidney) cells, CEF (chick embryo fibroblast) cells or MRC5 cells.

EXAMPLES

Cell Culture

Vero cells were maintained in DMEM Glutamax (Gibco-BRL) supplemented with 5% heat-inactivated fetal calf serum (FCS, Invitrogen, Frederick, Md.). Stable HEK293-17-MV helper cells used for viral rescue (WO2004/000876) were grown in DMEM supplemented with 10% FCS.

Construction and Rescue of Recombinant MV Vectors

The plasmid pTM-MVSchw, which contains an infectious MV cDNA corresponding to the anti-genome of the Schwarz MV vaccine strain, has been previously described (Combredet et al., *J Virol.,* 2003, 77(21): 11546-11554). The synthetic cDNA encoding for the polyepitopic construct of non-structural proteins from DENV1 was inserted into BsiWI/BssHII-digested pTM-MVSchw vectors in different positions, in combination or not with tetrameric EDIII antigen previously described (Brand/er et al., *PLoS* 2007, 1(3), e96; Brandler et al., *Vaccine,* 2010, 28, 6730-6739) (FIG. **7**). Rescue of recombinant viruses was performed as previously described (Combredet et al., *J Virol.,* 2003, 77(21): 11546-11554) using stable HEK293-T7-MV helper cells (WO2004/000876). The recombinant viruses were grown on Vero cells and viral titers were determined by end point dilution assay on Vero cells.

Western Blot

To evidence the expression of DENV antigens by MV vectors or pcDNA3 expression plasmid, lysates from Vero cells infected with MV-DENV or from HEK293 cells transfected with pcDNA3-NS plasmid were fractionated by SDS-PAGE, transferred to cellulose membranes (Amersham Pharmacia Biotech), and probed with anti-EDIII DENV1 mAb 4E11 or anti-NS3 antibody. A goat anti-mouse IgG-horseradish peroxidase (HRP) conjugate (Amersham) was used as secondary antibody. Peroxidase activity was visualized with an enhanced chemiluminescence detection kit (Pierce). This analysis showed that MV vectors expressed both EDIII tetrameric antigen and NS polyepitopic antigen. Similarly, the pcDNA3-NS plasmid expressed a high level of NS polyepitopic antigen (FIG. **8**).

Mice Experiments and Cellular Immune Responses

Mice deficient for IFNα/β receptors and expressing human MV receptor (hCD46+/− IFNα/β−/− or CD46-IFNAR) were produced as previously described (Combredet et al., *J Virol.,* 2003, 77(21): 11546-11554) and housed under pathogen-free conditions at the Institut Pasteur animal facility. Experiments were conducted following the guidelines of the Office of Laboratory Animal Care at Institut Pasteur. Group of six 6-week-old CD46-IFNAR mice were inoculated via the intraperitoneal (ip) route with a single administration of 10^5 TCID50 of MV-DENV vectors or empty MV. Mice were euthanized 7 days post-immunization and spleens were collected. Freshly extracted splenocytes were specifically stimulated for 18 h with DENV peptides (2 μg/ml) or MV (MOI 1). Cells were also stimulated by concanavalin A (5 μg/ml, Sigma) as a positive control and by RPMI-IL-2 (10 U/ml) as a negative control. Their capacity to secrete IFN-γ upon stimulation was tested by ELISPOT assay as previously described (Guerbois et al., *Virology,* 2009, 388(1): 191-203).

Peptides

A series of 36 overlapping peptides (9 to 15 amino acids overlapping of 5 amino acids) covering the entire NS polyepitopic sequence were synthesized (FIG. **9**). Five specific peptides were also identified with prediction algorithms able to bind to H2-Db and H2-Kb T cell receptors expressed in CD46-IFNAR mice (FIG. **9**). These peptides were used in ELISPOT experiments either in pools or as individual peptides to restimulate T cell responses in splenocytes from immunized CD46-IFNAR mice.

Immunogenicity in CD46-IFNAR Mice

Cell-mediated immune response (CMI) elicited by immunization with MV-DENV was assessed using IFN-γ ELISPOT assay on splenocytes collected 7 days after a single immunization. After ex vivo stimulation by DENV NS peptides or MV, a significant number of DENV-specific IFN-γ secreting cells (400-800 spot forming cells/10^6 splenocytes) were detected in MV-DENV immunized mice (FIGS. **10**, **11**, **12**), which represented one third of MV-specific response in similar stimulation condition (1500 spot forming cells/10^6 splenocytes). Most mice immunized with MV-DENV (5/6) had a significant CMI response to DENV, demonstrating that a single MV-DENV immunization in this experimental model was able to prime anti-DENV cellular immunity within a week.

Immunogenicity in Humanized Mice.

The pcDNA3 plasmid expressing the DENV1 NS polyepitope sequence under a CMV promoter was injected by electroporation in HLA-A*02-01, HLA-A*24:02, HLA-B*07:02 and HLA-B*35:01 monochain transgenic/H-2 Class I null mice, and the INF-γ response of spleen cells was quantified by ELISPOT assay against individual peptides (FIG. **13**).

Among 47 potential epitopes described to elicit an HLA-restricted T cell response in human donors previously exposed to DENV, 13 epitopes were identified in immunized mice: four in the first domain of NS3, and restricted by HLA-A*02:01, HLA-B*07:02 and HLA-13*35:01, four in the second domain of NS3, restricted by HLA-A*24:02 and HLA-B*35:01, three in NS4b, restricted by HLA-A*24:02 and HLA-B*35:01, and two in NS5 and restricted by HLA-A*02:01 and HLA-B*07:02 (FIG. **14**).

Comparison of the T cell response elicited in the different transgenic mice revealed a higher number of peptides with a higher magnitude in the HLA-B*35:01 mice, in agreement with the high response frequency and magnitude associated with this allele in human donors from hyperendemic area (Weiskopf D et al., *Proc Natl Acad Sci USA* 2013, 110(22): E2046-2053) (FIG. **15**).

Interestingly, and in agreement with the conserved antigenic regions selected from the different serotypes (FIGS. **1** and **14**), the amino acid sequence of the antigenic epitopes present in the polyepitopic construct was conserved among the other dengue serotypes, in particular for the two anchor residues involved in HLA binding (Table 3). This suggested that the CD8+ T cells induced by the DENV1-based construct could also recognize peptides derived from DENV2, 3 and 4. This T-cell cross reactivity may be verified using human EBV-transformed B cell line C1R (Zemmour J et al., *J Immunol* 1992, 148(6):1941-1948) expressing a single HLA allele, and pulsed with the cognate peptide, or infected with DENV1, 2, 3 and 4.

Evidence of an In Vitro and In Vivo Immune Protection Induced after DNA Immunization with the DENV1-NS Polyepitopic Construct (SEQ ID NO: 3)

A. Induction of DENV-Specific Cytotoxic T Cells in HLA Class I Transgenic Mice.

To investigate a role of CD8 T cells in a protective immune response, four groups of H-2 Class I null/HLA Class I transgenic mice (HLA-A*02:01, HLA-A*24:02, HLA-B*07:02 and HLA-B*35:01) were vaccinated by DNA immunization. In each group made up of seven transgenic animals, five and two mice received the DENV1-NS polyepitopic construct and the control plasmid, respectively. All animals were immunized by intradermic injection (100 μg DENV1-NS polyepitopic or control plasmid) followed by in vivo electroporation. Two immunizations were performed at three weeks interval, and spleen cells were tested for in vitro and in vivo cytotoxic activity as well as IFN-γ secretion by ELISPOT assay ten days after the second injection.

1—Evaluation of DENV-Specific Cytotoxic T Cell Responses In Vitro.

In each group of HLA Class I transgenic animals, three and one mouse that received the DENV1-NS polyepitopic construct and the control plasmid, respectively, were tested for their antigen-specific cytotoxic T cell responses. Quantification of the T cell response was obtained using the Granzyme B (GrB) ELISPOT assay, which measures at a single cell level the release of the cytotoxic mediator Granzyme B, and which was shown to correlate strongly with the ability of T cells to lyse target cells (Ewen C L et al., 2006, J Immunol Methods, 308(1-2): 156-166; Kalia V et al., 2010, Adv Exp Med Biol, 684: 79-95; Zanetti M, et al. 2010, Adv Exp Med Biol, 684:108-125) and to inhibit viral production (Marcet-Palacios M, et al., 2011, *PLoS Pathog,* 7(12):e1002447). In this assay, the frequency of spleen cells releasing Granzyme B upon in vitro stimulation with cognate or irrelevant peptides was measured in parallel with the frequency of cells secreting IFN-γ. Results showed a significant INF-γ and GrB response in mice immunized with the DENV1-NS polyepitopic construct, in comparison to the animals immunized with the control pcDNA3.1 plasmid (FIGS. **16**A and **16**B). There was also a correlation between the IFN-γ response and the release of GrB, with the highest response for both IFN-γ and GrB obtained for peptides P32 in HLA-A24 mice, P56 in HLA-A2 mice, P15 in HLA-B7 mice, and P49, P50 and P51 in HLA-B35 mice.

2—Evaluation of DENV-Specific Cytotoxic T Cells In Vivo.

The in vivo cytotoxic assay was performed as previously described (Clemente T. et al., 2013, *Methods,* 61(2):105-109). Briefly, mice immunized with the DENV1-NS polyepitopic construct or the control plasmid were adoptively transferred with syngeneic cells loaded with peptides and labeled with a fluorescent dye (Cell trace violet). A mix of 10^7 high- and 10^7 low-fluorescent stained cells, pulsed with specific and control peptides, respectively, was injected intravenously into recipient animals. Eighteen hours after the injection, spleen cells of recipient mice were analyzed by flow cytometry and the ratio between Cell trace high (cells pulsed with a mix of specific peptides) and Cell trace low donor cells (not pulsed or pulsed with control peptides) was determined. As an equivalent number of high and low stained cells were injected into recipient mice, a specific killing activity in immunized mice resulted in a lower fraction of high stained cells loaded with the mix of specific peptides (FIG. **17**). The percentage of specific lysis was determined using the formula:

$$1 - \frac{\%\ \text{Cell trace violet high immunized} / \%\ \text{Cell trace violet low immunized}}{\%\ \text{Cell trace violet high naive} / \%\ \text{Cell trace violet low naive}} \times 100$$

B. Induction of a Protective Immune Response in Humanized Mice

Because type I IFN-sufficient mice are resistant to DENV infection, a vaccine-induced protective immune response against a challenge with DENV can only be considered in type I-deficient mice, or in alymphoid mice engrafted with human hematopoietic stem cells. In line with the recent development of new generations of humanized mice reconstituted with human myeloid and lymphoid compartments with HLA-restricted responses (Legrand N, et al., 2011, *Proc Natl Acad Sci USA,* 108(32): 13224-13229; Garcia S, et al., 2012, *Immunol Lett,* 146(1-2): 1-7; Serra-Hassoun M, et al., 2014, *J Immunol,* 193(3): 1504-1511), the inventors will use $RAG^{-/-}$ $\gamma c^{-/-}$ mice transgenic for human SIRPalpha, in which mouse MHC class I and class II molecules have been replaced by human HLA-A2 and DR1 molecules, respectively (CH1-2hSa).

In a first setting, HLA-A2 molecules will be in the HHD configuration (with the human α1 and α2 domains of HLA-A2 linked to the murine α3 domain of H-2Db) (Pascolo S, et al., 1997, *J Exp Med,* 185(12): 2043-2051). The CH1-2hSa HHD mice are currently available. Three months after human hematopoietic cord blood progenitor engraftment, when all the human subsets have been reconstituted in the host, the mice will first be infected with Dengue virus to verify the in vivo viral replication in the human dendritic cell compartment. Briefly, two groups of three mice each will be injected intravenously with 10^5 or 10^6 PFU of the DENV1 strain KDH0026A (derived from a human clinical isolate). Virus titers will be monitored by quantitative reverse transcription (qRT)-PCR.

In a second setting, the HLA-A2 molecules will consist of the full human HHH version of the class I molecule. These new CH1-2hSa HHH hosts, which are currently under development, should improve the binding of the human CD8/TCR molecules to the MHC-peptide complexes allowing a more efficient stimulation of DENV-specific CD8 T cells. Two groups of 6 humanized CH1-2hSa HHH mice each will be immunized with the DENV1-NS polyepitopic and the control plasmid constructs, as described in FIG. **13**. Within each group of 6 reconstituted mice, protection will be assessed by quantifying viral mRNA by qRT-PCR in the blood of infected animals at day 2, 4 and 7 after intravenous injection of 10^5 or 10^6 PFU of DENV1 strain KDH0026A within each group of three mice.

C. MVDVax Protective Efficacy in CD46-IFNAR Mice

The inventors evaluated the protective efficacy in CD46-IFNAR mice of recombinant MVDVax vectors expressing a tetravalent DENV antigen composed of the fusion of the envelope domain III (EDIII) of the four DENV serotypes fused to the ectodomain of the membrane protein (ectoM) of DENV1 and expressing simultaneously the DENV1 NS antigen of the invention (described in FIG. **7**). CD46-IFNAR mice were produced as previously described (Combredet, C. et al., 2003, *J Virol,* 77(21): 11546-11554) and housed under pathogen-free conditions at the Institut Pasteur animal facility. Experiments were conducted following the guidelines of the Office of Laboratory Animal Care at Institut Pasteur. Group of six 6-week-old CD46-IFNAR mice were inoculated via the intraperitoneal (ip) route with 10^5 TCID50 of

MV-DENV vectors or empty MV. A second administration of the same dose was performed 1 month after priming. To analyze the presence of anti-MV and anti-DENV antibodies, blood was regularly collected by the periorbital route. Two months after the last immunization, all animals were experimentally challenged by intraperitoneal injection of 10^5 TCID50 of mouse-neuro adapted DENV1 Hawaï strain grown on Vero cells (Despres et al, *J. Virol.,* 1998, 72(1), 823-829). After challenge, blood was collected by the periorbital route at day 1, 2, 3, 5, 7 and the animals were followed for clinical signs and weight for the 15 following days. DENV1 genomic viral load was determined in mice sera by one-step qRT-PCR as described below. Sera were heat inactivated at 56° C. for 30 min and the presence of anti-MV antibodies was detected using ELISA (Trinity Biotech). HRP-conjugated anti-mouse immunoglobulin (Jackson Immuno Research) was used as secondary antibody. Anti-DENV antibodies were detected as previously described (Brandler et al., Vaccine, 2010, 28, 6730-6739) by ELISA using 96-well plates coated with recombinant EDIII proteins from DENV1, DENV2, DENV3, and DENV4 produced in *E. coli* or synthesized in vitro. HRP-conjugated anti-mouse immunoglobulin was used as secondary antibody. The endpoint titers of pooled sera were calculated as the reciprocal of the last dilution giving twice the absorbance of sera from MV inoculated mice that served as negative controls.

D. MVDVax Protective Efficacy in Non-Human Primates

The inventors will evaluate in non-human primates (NHP) the protective efficacy of recombinant MVDVax vectors.

Experiments will be conducted as follows:

Viruses.

Challenge viruses: DENV1 Jamaica strain CVI 1636 3P, isolated in 1977, passages 2/3 MP/3P C6/36HT 2P Vero cells culture supernatant. DENV1 strain KDH0026A, C6/36 cell culture supernatant. DENV2 DJ.M.O.1.7.12, C6/36 cell culture supernatant. DENV4 Dominica 814669 strain, isolated in 1981, passages 4P C6/36 HT 2P Vero cells culture supernatant. These viruses are used for neutralization tests. The recombinant MVDVax vaccine virus is prepared as previously described (Brandler et al., *Vaccine,* 2010, 28, 6730-6739) and viral titer is determined by endpoint limit-dilution assay on Vero cells.

Animals.

Mauritian-derived cynomolgus macaques (*Macaca fascicularis*) are housed in BSL-3 animal care facility at the CEA. The Ile-de-France region ethics committee will approve experimental methods that are conducted in accordance with the European Directive 2010-63-UE. The animals are juvenile male and female adults (0.8-1 kg). To evaluate the immunogenicity of the vaccine candidate, 12 animals are inoculated subcutaneously with two 200-μL doses containing 10^5 TCID50 of MVDvax vaccine virus one month apart and are boosted six month later with a third dose of 10^6 TCID50 of MVDVax. Similarly, eight control animals receive two administrations of empty MVSchw vaccine (200 μL containing 10^5 TCID50) and a third dose of 10^6 TCID50 six months later. Five months after the last immunization, the animals are divided in two groups and challenged by intravenous inoculation of 1.0×10^4 pfu of wild type DENV1 or DENV4 suspended in 200 μL PBS. Monkeys are monitored for viremia, clinical signs, and cellular and antibody response. Peripheral blood mononuclear cells (PBMC) are isolated by Percoll density gradient centrifugation (Sigma-Aldrich). Serum and plasma are collected and stored at −20° C. for later analysis.

Humoral Responses.

Anti-DENV and anti-MV antibodies are detected in heat-inactivated sera by use of an enzyme-linked immunosorbant assay (ELISA) as previously described (Brand/er et al., *Vaccine,* 2010, 28, 6730-6739). Sera are considered positive when the optical density (OD) is twice the OD of sera from control animals.

DENV Neutralization Test.

Anti-DENV neutralizing antibodies are detected using a focus reduction neutralization test (PRNT) in Vero cells as previously described (Brandler et al., *PLoS* 2007, 1(3), e96). Briefly, anti-DENV neutralizing antibodies are detected on Vero cells using 50 FFU of Vero-adapted DENV1 Hawaï strain (WHO reference strain, Genbank accession no. AF226687), DENV2 Jamaica strain N.1409, DENV3 strain PaH881/88 Thailand, or DENV4 strain 63632/76 Burma. The endpoint titer is calculated as the highest serum dilution that reduces the number of FFU by at least 50%. The neutralizing antibody titer is also tested at the Center for Vaccine Development (CVD, Mahidol University, Thailand). In the tests conducted at the CVD, monkey kidney-derived LLC-MK2 cells and the following DENV are used: DENV1 (16007), DENV2 (16681), DENV3 (16562), and DENV4 (1036), and the PRNT titer is calculated based on a 50% reduction in plaque count (PRNT50) as previously described (Sirivichayakul et al. *Virol. J.* 2014, 11-48).

Cellular Immune Responses.

Cellular responses are detected by Elispot assay and by polyfunctional flow cytometry following stimulation of lymphocytes from peripheral blood with synthetic peptide pools covering the DENV1-NS insert of MVDVax, as previously described (Stebbings et al, *PLoS-One,* 2012, 7(11), e50397). Cells are stimulated in triplicate with synthetic 15-mer (overlapping by 11aa) peptide pools (BEI, http://www.beiresources.org) at 1 μg/ml/peptide or a live-attenuated empty MV at 10^4 TCID50/10^6 cells, in the presence of 1 μg/ml of the co-stimulatory antibodies anti-CD28 and CD49d (Biolegend). Negative controls are incubated with an equal volume of DMSO (0.15% v/v) without peptide and positive controls with 1 μg/ml Staphylococcal Enterotoxin B (Sigma-Aldrich).

Quantification of DENV Viral RNA and DENV Titration.

Sera (25 μL) are diluted in 0.5 mL Dulbecco's modified Eagle's medium (DMEM)/5% fetal calf serum (FCS). Viral RNA is extracted (QlAamp viral RNA extraction kit, Qiagen) and analyzed by one step DENV qRT-PCR, using high fidelity enzymes (Roche, Mannheim, Germany). Real-time qRT-PCR of DENV RNA is performed with RealArt™ WNV LC real-time PCR kit (Qiagen). For virus titration, samples are diluted in 250 μL of medium, and infectivity of serial dilutions is assayed on Vero cells overlaid with DMEM Glutamax/2% FCS containing 0.8% final (weight/volume) carboxy methylcellulose. After 4 days of incubation, cells are fixed and plaques are visualized by an immuno-focus assay as previously described (Brandler et al., *PLoS* 2007, 1(3), e96).

SEQUENCE LISTING

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<220> FEATURE:
<223> OTHER INFORMATION: Native nucleotide sequence of the
polynucleotide encoding the chimeric polyepitope of DENV1

<400> SEQUENCE: 1

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<210> SEQ ID NO 2
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<223> OTHER INFORMATION: Optimised nucleotide sequence of the
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codon optimised, measles optimised)

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the chimeric polyepitope of DENV1

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Arg Arg Tyr Leu Pro Ala Ile Val Arg Glu Ala Ile Lys Arg Lys Leu
        35                  40                  45

Arg Thr Leu Ile Leu Ala Pro Thr Arg Val Val Ala Ser Glu Met Ala
    50                  55                  60

Glu Ala Leu Lys Gly Met Pro Ile Arg Tyr Gln Thr Thr Ala Val Lys
65                  70                  75                  80
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Ser Glu His Thr Gly Lys Glu Ile Val Asp Leu Met Cys His Ala Thr
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Phe Thr Met Arg Leu Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Met
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Ile Ile Met Asp Glu Ala His Phe Thr Asp Pro Ser Ser Ile Ala Ala
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Arg Gly Tyr Ile Ser Thr Arg Val Gly Met Gly Glu Ala Ala Ala Ile
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145                 150                 155                 160

Asn Ala Val Ile Gln Asp Glu Glu Arg Asp Ile Pro Glu Arg Ser Trp
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Asn Ser Gly Tyr Glu Trp Ile Thr Asp Glu Asp His Ala His Trp Thr
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Glu Ala Lys Met Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile
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Pro Ala Leu Phe Glu Pro Glu Arg Glu Lys Ser Ala Ala Ile Asp Gly
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Glu Tyr Arg Leu Arg Gly Glu Ala Arg Lys Thr Phe Val Glu Leu Met
225                 230                 235                 240

Arg Arg Gly Asp Leu Pro Val Trp Leu Ser Tyr Lys Val Ala Ser Glu
                245                 250                 255

Gly Phe Gln Tyr Ser Asp Arg Arg Trp Cys Phe Asp Gly Glu Arg Asn
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Asn Gln Val Leu Glu Glu Asn Met Asp Val Glu Ile Trp Thr Lys Glu
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Gly Glu Arg Lys Lys Leu Arg Pro Arg Trp Leu Asp Ala Arg Thr Tyr
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Ser Asp Pro Leu Ala Leu Arg Glu Phe Lys Glu Phe Ala Ala Gly Val
305                 310                 315                 320

Ala Val Glu Asn His His His Ala Ala Met Leu Asp Val Asp Leu His
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Pro Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Ile Ile Thr
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Pro Met Met Arg His Thr Ile Glu Asn Thr Thr Ala Asn Ile Ser Leu
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Thr Ala Ile Ala Asn Gln Ala Ala Ile Leu Met Gly Leu Asp Lys Gly
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Trp Pro Ile Ser Lys Met Asp Ile Gly Val Pro Leu Leu Ala Leu Gly
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Cys Tyr Ser Gln Val Leu Asp Ile Ile Gly Gln Arg Ile Glu Asn Ile
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Lys His Glu His Lys Ser Thr Trp His Tyr Asp Glu Asp Asn Pro Tyr
            420                 425                 430

Lys Thr Trp Ala Tyr His Gly Ser Tyr Glu Val Lys Pro Ser Gly Ser
        435                 440                 445

Ala Ser Ser Met Val Asn Gly Val Val Lys Leu Leu Thr Lys Pro Trp
    450                 455                 460

Asp Val Ile Pro Met Val Thr Gln Ile Ala Met Thr Asp Thr Thr Pro
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Phe Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr Pro
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Lys Ala Lys Arg Gly Thr Ala Gln Ile Met Glu Val Thr Ala Lys Trp
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Glu Glu Phe Thr Arg Lys Val Arg Ser Asn Ala
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Native nucleotide sequence of the polynucleotide encoding the first region of NS3 of DENV1

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tccgaaatgg cagaggcgct caagggaatg ccaataaggt accaaacaac agcagtgaag 240

agtgaacaca caggaaaaga gatagttgac ctcatgtgcc acgccacttt caccatgcgt 300

ctcctgtctc ccgtgagagt tcccaattac aacatgatta ttatggatga agcacatttc 360

accgatccat ccagtatagc agccagaggg tacatctcaa cccgagtggg catgggtgaa 420

gcagctgcga tcttcatgac agccactcct ccaggatcag tggaggcctt tccacagagc 480

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<211> LENGTH: 555
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<220> FEATURE:
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tccgaaatgg ctgaggccct gaaaggcatg cccatccggt atcagaccac agcagtgaag 240

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ctgctgagcc cagtgcgggt ccccaactac aatatgatca ttatggacga ggcccacttt 360

actgatccca gctccatcgc cgctagagga tatatttcca ccagggtggg aatgggcgag 420

gcagcagcta tcttcatgac agcaactccc cctggcagcg tggaggcatt tcctcagtcc 480

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Lys Arg Asn Leu Thr Ile Met Asp Leu His Pro Gly Ser Gly Lys Thr
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Arg Arg Tyr Leu Pro Ala Ile Val Arg Glu Ala Ile Lys Arg Lys Leu
35 40 45

Arg Thr Leu Ile Leu Ala Pro Thr Arg Val Val Ala Ser Glu Met Ala
50 55 60

Glu Ala Leu Lys Gly Met Pro Ile Arg Tyr Gln Thr Thr Ala Val Lys
65 70 75 80

Ser Glu His Thr Gly Lys Glu Ile Val Asp Leu Met Cys His Ala Thr
85 90 95

Phe Thr Met Arg Leu Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Met
100 105 110

Ile Ile Met Asp Glu Ala His Phe Thr Asp Pro Ser Ser Ile Ala Ala
115 120 125

Arg Gly Tyr Ile Ser Thr Arg Val Gly Met Gly Glu Ala Ala Ala Ile
130 135 140

Phe Met Thr Ala Thr Pro Pro Gly Ser Val Glu Ala Phe Pro Gln Ser
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Asn Ala Val Ile Gln Asp Glu Glu Arg Asp Ile Pro Glu Arg Ser Trp
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Asn Ser Gly Tyr Glu Trp Ile Thr Asp
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Native nucleotide sequence of the polynucleotide encoding the second region of NS3 of DENV1

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ccagtttggc tatcttacaa agttgcctca gaaggcttcc aatactccga tagaaggtgg 240

tgctttgatg gagaaaggaa caaccaggtg ttggaggaaa acatggacgt ggagatctgg 300

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cccgtgtggc tgagttacaa ggtcgcttca gagggattcc agtatagtga ccgacggtgg 240

tgctttgatg gcgaacgcaa caatcaggtg ctggaggaga acatggatgt cgagatttgg 300

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Lys Ser Ala Ala Ile Asp Gly Glu Tyr Arg Leu Arg Gly Glu Ala Arg
35 40 45

Lys Thr Phe Val Glu Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu
50 55 60

Ser Tyr Lys Val Ala Ser Glu Gly Phe Gln Tyr Ser Asp Arg Arg Trp
65 70 75 80

Cys Phe Asp Gly Glu Arg Asn Asn Gln Val Leu Glu Glu Asn Met Asp
85 90 95

Val Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys Lys Leu Arg Pro Arg
100 105 110

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Lys Glu Phe Ala Ala Gly
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<210> SEQ ID NO 10
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Native nucleotide sequence of the polynucleotide encoding the NS4b fragment of DENV1

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gcctggaccc tctatgcagt ggccacaaca attatcactc ccatgatgag gcacacaata 120

gaaaacacaa cggcaaacat ttccctgaca gccattgcaa accaggcggc tatattgatg 180

ggacttgaca aaggatggcc aatatcgaag atggacatag gagttccact tctcgccttg 240

gggtgctatt cccaggtg 258

<210> SEQ ID NO 11
<211> LENGTH: 258
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Optimised nucleotide sequence of the polynucleotide encoding the NS4b fragment of DENV1

<400> SEQUENCE: 11

gtggccgtcg agaatcacca tcacgccgct atgctggacg tggatctgca tcctgccagt 60

gcttggaccc tgtatgcagt ggccactacc atcattaccc caatgatgcg ccacacaatc 120

gagaacacaa ctgccaatat ctcactgaca gctattgcaa accaggcagc cattctgatg 180

ggactggaca aaggctggcc catcagcaag atggatattg gcgtgcctct gctggccctg 240

gggtgttaca gtcaggtg 258

<210> SEQ ID NO 12
<211> LENGTH: 86
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the NS4b fragment of DENV1

<400> SEQUENCE: 12

Val Ala Val Glu Asn His His His Ala Ala Met Leu Asp Val Asp Leu
1 5 10 15

His Pro Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Ile Ile
20 25 30

Thr Pro Met Met Arg His Thr Ile Glu Asn Thr Thr Ala Asn Ile Ser
35 40 45

Leu Thr Ala Ile Ala Asn Gln Ala Ala Ile Leu Met Gly Leu Asp Lys
50 55 60

Gly Trp Pro Ile Ser Lys Met Asp Ile Gly Val Pro Leu Leu Ala Leu
65 70 75 80

Gly Cys Tyr Ser Gln Val
85

<210> SEQ ID NO 13
<211> LENGTH: 402
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Native nucleotide sequence of the polynucleotide encoding the NS5 fragment of DENV1

<400> SEQUENCE: 13

ctggatatca ttggccagag gatagagaac ataaaacatg aacataagtc aacatggcat 60

tatgatgagg acaatccata taaaacatgg gcctatcacg gatcatatga ggtcaagcca 120

tcaggatcag cctcatccat ggtcaatggc gtggtgaaac tgctcaccaa accatgggat 180

gtcatcccca tggtcacaca aatagccatg actgacacca cacccttgg acaacagagg 240

gtgttcaaag agaaagttga cacgcgcaca ccaaaagcaa aacgaggcac agcacaaatc 300

atggaggtga cagccaaatg gttatggggt tttctttcta gaaacaaaaa accaagaatt 360

tgtacaagag aggagttcac aagaaaagtc aggtcaaacg ca 402

<210> SEQ ID NO 14
<211> LENGTH: 402
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Optimised nucleotide sequence of the polynucleotide encoding the NS5 fragment of DENV1

<400> SEQUENCE: 14

ctggacatca ttggccagag gatcgagaac attaagcatg agcacaaatc aacctggcat 60

tacgacgaag ataatcccta taagacatgg gcctaccacg gaagctatga ggtgaaacct 120

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tcaggcagcg ccagcagcat ggtcaacggg gtggtcaagc tgctgaccaa accttgggac 180

gtgatcccaa tggtcactca gattgccatg accgatacca ccccattcgg ccagcagcgg 240

gtgttcaagg agaaggtgga cacccgcaca cctaaggcta aacgagggac tgcacagatc 300

atggaggtga ccgccaagtg gctgtgggga ttcctgtcca ggaacaagaa gccaagaatc 360

tgtaccaggg aagagttcac aagaaaggtc cggtcaaacg cc 402

<210> SEQ ID NO 15
<211> LENGTH: 134
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the NS5 fragment of DENV1

<400> SEQUENCE: 15

Leu Asp Ile Ile Gly Gln Arg Ile Glu Asn Ile Lys His Glu His Lys
1 5 10 15

Ser Thr Trp His Tyr Asp Glu Asp Asn Pro Tyr Lys Thr Trp Ala Tyr
20 25 30

His Gly Ser Tyr Glu Val Lys Pro Ser Gly Ser Ala Ser Ser Met Val
35 40 45

Asn Gly Val Val Lys Leu Leu Thr Lys Pro Trp Asp Val Ile Pro Met
50 55 60

Val Thr Gln Ile Ala Met Thr Asp Thr Thr Pro Phe Gly Gln Gln Arg
65 70 75 80

Val Phe Lys Glu Lys Val Asp Thr Arg Thr Pro Lys Ala Lys Arg Gly
85 90 95

Thr Ala Gln Ile Met Glu Val Thr Ala Lys Trp Leu Trp Gly Phe Leu
100 105 110

Ser Arg Asn Lys Lys Pro Arg Ile Cys Thr Arg Glu Glu Phe Thr Arg
115 120 125

Lys Val Arg Ser Asn Ala
130

<210> SEQ ID NO 16
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P20 epitope

<400> SEQUENCE: 16

Leu Pro Glu Ile Glu Asp Glu Val Phe
1 5

<210> SEQ ID NO 17
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P19 epitope

<400> SEQUENCE: 17

His Pro Gly Ser Gly Lys Thr Arg Arg Tyr
1 5 10

<210> SEQ ID NO 18
<211> LENGTH: 11
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P30 epitope

<400> SEQUENCE: 18

Arg Tyr Leu Pro Ala Ile Val Arg Glu Ala Ile
1 5 10

<210> SEQ ID NO 19
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P451 epitope

<400> SEQUENCE: 19

Tyr Leu Pro Ala Ile Val Arg Glu Ala
1 5

<210> SEQ ID NO 20
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P11 epitope

<400> SEQUENCE: 20

Leu Pro Ala Ile Val Arg Glu Ala Ile
1 5

<210> SEQ ID NO 21
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P36 epitope

<400> SEQUENCE: 21

Ala Pro Thr Arg Val Val Ala Ser Glu Met
1 5 10

<210> SEQ ID NO 22
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P48 EPITOPE

<400> SEQUENCE: 22

Glu Met Ala Glu Ala Leu Lys Gly Met Pro Ile Arg Tyr Gln Thr
1 5 10 15

<210> SEQ ID NO 23
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P12 epitope

<400> SEQUENCE: 23

Ser Pro Val Arg Val Pro Asn Tyr Asn Met
1 5 10

<210> SEQ ID NO 24
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P454 epitope

<400> SEQUENCE: 24

Val Pro Asn Tyr Asn Met Ile Ile Met
1 5

<210> SEQ ID NO 25
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P18 epitope

<400> SEQUENCE: 25

Asp Pro Ser Ser Ile Ala Ala Arg Gly Tyr
1 5 10

<210> SEQ ID NO 26
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P457 epitope

<400> SEQUENCE: 26

Ala Val Ile Gln Asp Glu Glu Arg Asp Ile
1 5 10

<210> SEQ ID NO 27
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P453 epitope

<400> SEQUENCE: 27

Arg Ser Trp Asn Ser Gly Tyr Glu Trp
1 5

<210> SEQ ID NO 28
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P49 epitope

<400> SEQUENCE: 28

Thr Pro Glu Gly Ile Ile Pro Ala Leu
1 5

<210> SEQ ID NO 29
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P28 epitope

<400> SEQUENCE: 29

Lys Thr Phe Val Glu Leu Met Arg Arg
1 5

<210> SEQ ID NO 30
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Amino acid sequence of the P2 epitope

<400> SEQUENCE: 30

Glu Leu Met Arg Arg Gly Asp Leu Pro Val
1 5 10

<210> SEQ ID NO 31
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P450 epitope

<400> SEQUENCE: 31

Asp Leu Met Arg Arg Gly Asp Leu Pro Val
1 5 10

<210> SEQ ID NO 32
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P50 epitope

<400> SEQUENCE: 32

Leu Pro Val Trp Leu Ser Tyr Lys Val Ala
1 5 10

<210> SEQ ID NO 33
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P32 epitope

<400> SEQUENCE: 33

Gln Tyr Ser Asp Arg Arg Trp Cys Phe
1 5

<210> SEQ ID NO 34
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P73 epitope

<400> SEQUENCE: 34

Asn Tyr Ala Asp Arg Arg Trp Cys Phe
1 5

<210> SEQ ID NO 35
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P74 epitope

<400> SEQUENCE: 35

Asn Tyr Ala Asp Arg Lys Trp Cys Phe
1 5

<210> SEQ ID NO 36
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P75 epitope

<400> SEQUENCE: 36

Lys Tyr Thr Asp Arg Lys Trp Cys Phe
1 5

<210> SEQ ID NO 37
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P76 epitope

<400> SEQUENCE: 37

Ser Tyr Lys Asp Arg Glu Trp Cys Phe
1 5

<210> SEQ ID NO 38
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P35 epitope

<400> SEQUENCE: 38

Arg Pro Arg Trp Leu Asp Ala Arg Thr
1 5

<210> SEQ ID NO 39
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P17 epitope

<400> SEQUENCE: 39

Leu Asp Ala Arg Thr Tyr Ser Asp Pro Leu Ala Leu Arg Glu Phe Lys
1 5 10 15

Glu Phe

<210> SEQ ID NO 40
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P29 epitope

<400> SEQUENCE: 40

Arg Ile Tyr Ser Asp Pro Leu Ala Leu Lys
1 5 10

<210> SEQ ID NO 41
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P452 epitope

<400> SEQUENCE: 41

Arg Thr Tyr Ser Asp Pro Leu Ala Leu Arg
1 5 10

<210> SEQ ID NO 42
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Amino acid sequence of the P21 epitope

<400> SEQUENCE: 42

His Pro Ala Ser Ala Trp Thr Leu Tyr
1 5

<210> SEQ ID NO 43
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P16 epitope

<400> SEQUENCE: 43

Pro Ala Ser Ala Trp Thr Leu Tyr
1 5

<210> SEQ ID NO 44
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P13 epitope

<400> SEQUENCE: 44

His Pro Ala Ser Ala Trp Thr Leu Tyr Ala
1 5 10

<210> SEQ ID NO 45
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P51 epitope

<400> SEQUENCE: 45

Thr Leu Tyr Ala Val Ala Thr Thr Ile
1 5

<210> SEQ ID NO 46
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P52 epitope

<400> SEQUENCE: 46

Val Ala Thr Thr Ile Ile Thr Pro Met
1 5

<210> SEQ ID NO 47
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P33 epitope

<400> SEQUENCE: 47

Ile Thr Pro Met Met Arg His Thr Ile
1 5

<210> SEQ ID NO 48
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P14 epitope

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<400> SEQUENCE: 48

Thr Pro Met Met Arg His Thr Ile Glu Asn
1 5 10

<210> SEQ ID NO 49
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P22 epitope

<400> SEQUENCE: 49

Ile Ala Asn Gln Ala Ala Ile Leu Met
1 5

<210> SEQ ID NO 50
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P456 epitope

<400> SEQUENCE: 50

Ala Ala Ile Leu Met Gly Leu Asp Lys
1 5

<210> SEQ ID NO 51
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P53 epitope

<400> SEQUENCE: 51

Lys Met Asp Ile Gly Val Pro Leu Leu
1 5

<210> SEQ ID NO 52
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P54 epitope

<400> SEQUENCE: 52

Val Pro Leu Leu Ala Leu Gly Cys Tyr
1 5

<210> SEQ ID NO 53
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P55 epitope

<400> SEQUENCE: 53

Asp Asn Pro Tyr Lys Thr Trp Ala Tyr His
1 5 10

<210> SEQ ID NO 54
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P24 epitope

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<400> SEQUENCE: 54

Trp Ala Tyr His Gly Ser Tyr Glu Val
1 5

<210> SEQ ID NO 55
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P56 epitope

<400> SEQUENCE: 55

Ser Met Val Asn Gly Val Val Lys Leu
1 5

<210> SEQ ID NO 56
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P5 epitope

<400> SEQUENCE: 56

Leu Leu Thr Lys Pro Trp Asp Val Ile Pro Met Val Thr Gln Ile
1 5 10 15

<210> SEQ ID NO 57
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P6 epitope

<400> SEQUENCE: 57

Leu Leu Thr Lys Pro Trp Asp Val Ile Pro
1 5 10

<210> SEQ ID NO 58
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P7 epitope

<400> SEQUENCE: 58

Leu Thr Lys Pro Trp Asp Val Ile Pro Met
1 5 10

<210> SEQ ID NO 59
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P8 epitope

<400> SEQUENCE: 59

Thr Lys Pro Trp Asp Val Ile Pro Met Val
1 5 10

<210> SEQ ID NO 60
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P9 epitope

<400> SEQUENCE: 60

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Lys Pro Trp Asp Val Ile Pro Met Val Thr
1 5 10

<210> SEQ ID NO 61
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P10 epitope

<400> SEQUENCE: 61

Pro Trp Asp Val Ile Pro Met Val Thr Gln
1 5 10

<210> SEQ ID NO 62
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P27 epitope

<400> SEQUENCE: 62

Trp Asp Val Ile Pro Met Val Thr Gln Ile
1 5 10

<210> SEQ ID NO 63
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P455 epitope

<400> SEQUENCE: 63

Ile Pro Met Val Thr Gln Ile Ala Met
1 5

<210> SEQ ID NO 64
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P34 epitope

<400> SEQUENCE: 64

Asp Thr Thr Pro Phe Gly Gln Gln Arg
1 5

<210> SEQ ID NO 65
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P23 epitope

<400> SEQUENCE: 65

Thr Pro Phe Gly Gln Gln Arg Val Phe
1 5

<210> SEQ ID NO 66
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P3 epitope

<400> SEQUENCE: 66

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Thr Ala Lys Trp Leu Trp Gly Phe Leu Ser Arg Asn Lys Lys Pro Arg
1 5 10 15

Ile Cys Thr Arg
20

<210> SEQ ID NO 67
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P4 epitope

<400> SEQUENCE: 67

Trp Gly Phe Leu Ser Arg Asn Lys Lys
1 5

<210> SEQ ID NO 68
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the P15 epitope

<400> SEQUENCE: 68

Lys Pro Arg Ile Cys Thr Arg Glu Glu Phe
1 5 10

<210> SEQ ID NO 69
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 8-22 of the first region of NS3

<400> SEQUENCE: 69

Pro Glu Leu Glu Glu Glu Met Phe Lys Lys Arg Asn Leu Thr Ile
1 5 10 15

<210> SEQ ID NO 70
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 18-32 of the first region of NS3

<400> SEQUENCE: 70

Arg Lys Leu Thr Ile Met Asp Leu His Pro Gly Ser Gly Lys Thr
1 5 10 15

<210> SEQ ID NO 71
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 32-46 of the first region of NS3

<400> SEQUENCE: 71

Thr Lys Arg Tyr Leu Pro Ala Ile Val Arg Glu Ala Ile Lys Arg
1 5 10 15

<210> SEQ ID NO 72
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 33-42 of the first region of NS3

<400> SEQUENCE: 72

Arg Lys Tyr Leu Pro Ala Ile Val Arg Glu
1 5 10

<210> SEQ ID NO 73
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 36-50 of the first region of NS3

<400> SEQUENCE: 73

Leu Pro Ala Ile Val Arg Glu Ala Ile Lys Arg Arg Leu Arg Thr
1 5 10 15

<210> SEQ ID NO 74
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 40-54 of the first region of NS3

<400> SEQUENCE: 74

Val Arg Glu Ala Ile Lys Arg Arg Leu Arg Thr Leu Ile Leu Ala
1 5 10 15

<210> SEQ ID NO 75
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 56-66 of the first region of NS3

<400> SEQUENCE: 75

Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala
1 5 10

<210> SEQ ID NO 76
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 55-69 of the first region of NS3

<400> SEQUENCE: 76

Pro Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Met Lys Gly
1 5 10 15

<210> SEQ ID NO 77
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 66-80 of the first region of NS3

<400> SEQUENCE: 77

Ala Leu Lys Gly Met Pro Ile Arg Tyr Gln Thr Thr Ala Val Lys
1 5 10 15

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<210> SEQ ID NO 78
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 68-82 of the first region of NS3

<400> SEQUENCE: 78

Lys Gly Leu Pro Ile Arg Tyr Gln Thr Thr Ala Thr Lys Ser Glu
1 5 10 15

<210> SEQ ID NO 79
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 72-86 of the first region of NS3

<400> SEQUENCE: 79

Ile Arg Tyr Gln Thr Thr Ala Thr Lys Ser Glu His Thr Gly Arg
1 5 10 15

<210> SEQ ID NO 80
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 83-97 of the first region of NS3

<400> SEQUENCE: 80

His Thr Gly Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Glu
1 5 10 15

<210> SEQ ID NO 81
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 86-97 of the first region of NS3

<400> SEQUENCE: 81

Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Phe
1 5 10

<210> SEQ ID NO 82
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 87-96 of the first region of NS3

<400> SEQUENCE: 82

Glu Ile Val Asp Leu Met Cys His Ala Thr
1 5 10

<210> SEQ ID NO 83
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 89-98 of the first region of NS3

<400> SEQUENCE: 83

Val Asp Leu Met Cys His Ala Thr Phe Thr
1 5 10

<210> SEQ ID NO 84
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 96-110 of the first region of NS3

<400> SEQUENCE: 84

Thr Phe Thr Met Arg Leu Leu Ser Pro Val Arg Val Pro Asn Tyr
1 5 10 15

<210> SEQ ID NO 85
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 108-122 of the first region of NS3

<400> SEQUENCE: 85

Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu Ala His Phe Thr Asp
1 5 10 15

<210> SEQ ID NO 86
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 124-138 of the first region of NS3

<400> SEQUENCE: 86

Ala Ser Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Gly Met
1 5 10 15

<210> SEQ ID NO 87
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 139-154 of the first region of NS3

<400> SEQUENCE: 87

Glu Ala Ala Ala Ile Phe Met Thr Ala Thr Pro Pro Gly Thr Ala
1 5 10 15

<210> SEQ ID NO 88
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 287-301 of the second region of NS3

<400> SEQUENCE: 88

Arg Glu Gly Glu Lys Lys Lys Leu Arg Pro Arg Trp Leu Asp Arg
1 5 10 15

<210> SEQ ID NO 89
<211> LENGTH: 15
<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 307-319 of the second region of NS3

<400> SEQUENCE: 89

Pro Leu Ala Leu Lys Glu Phe Lys Asp Phe Ala Ala Gly Arg Lys
1 5 10 15

<210> SEQ ID NO 90
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 417-433 of NS5

<400> SEQUENCE: 90

Lys Glu Glu His Ser Ser Thr Trp His Tyr Asp Asp Glu Asn Pro Tyr
1 5 10 15

Lys

<210> SEQ ID NO 91
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 423-439 of NS5

<400> SEQUENCE: 91

Thr Trp His Tyr Asp Asp Glu Asn Pro Tyr Lys Thr Trp Ala Tyr His
1 5 10 15

Gly

<210> SEQ ID NO 92
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 427-444 of NS5

<400> SEQUENCE: 92

Asp Glu Asn Pro Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr Glu Val
1 5 10 15

Lys

<210> SEQ ID NO 93
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 433-447 of NS5

<400> SEQUENCE: 93

Lys Thr Trp Ala Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly
1 5 10 15

<210> SEQ ID NO 94
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position

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451-473 of NS5

<400> SEQUENCE: 94

Ser Met Ile Asn Gly Val Val Lys Leu Leu Thr Lys Pro Trp Asp Val
1 5 10 15

Val

<210> SEQ ID NO 95
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 462-471 of NS5

<400> SEQUENCE: 95

Lys Pro Trp Asp Val Leu Pro Met Val
1 5

<210> SEQ ID NO 96
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 457-463 of NS5

<400> SEQUENCE: 96

Val Lys Leu Leu Thr Lys Pro Trp Asp Val Val Pro Met Val Thr Gln
1 5 10 15

Met

<210> SEQ ID NO 97
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the peptide at position 469-485 of NS5

<400> SEQUENCE: 97

Met Val Thr Gln Met Ala Met Thr Asp Thr Thr Pro Phe Gly Gln Gln
1 5 10 15

Arg Val

<210> SEQ ID NO 98
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 98

Val Lys Ser Glu His Thr Gly Lys Glu Ile Val Asp Leu Met Cys
1 5 10 15

<210> SEQ ID NO 99
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 99

His Thr Gly Lys Glu Ile Val Asp Leu Met Cys His Ala Thr Phe

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1 5 10 15

<210> SEQ ID NO 100
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 100

Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg Leu
1 5 10 15

<210> SEQ ID NO 101
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 101

Leu Met Cys His Ala Thr Phe Thr Met Arg Leu Leu Ser Pro Val
1 5 10 15

<210> SEQ ID NO 102
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 102

Ala Thr Phe Thr Met Arg Leu Leu Ser Pro Val Arg Val Pro Asn
1 5 10 15

<210> SEQ ID NO 103
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 103

Met Arg Leu Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Met Ile
1 5 10 15

<210> SEQ ID NO 104
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 104

Glu Phe Lys Glu Phe Ala Ala Gly Val Ala Val Glu Asn His His
1 5 10 15

<210> SEQ ID NO 105
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 105

Phe Ala Ala Gly Val Ala Val Glu Asn His His His Ala Ala Met
1 5 10 15

<210> SEQ ID NO 106
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 106

Val Ala Val Glu Asn His His His Ala Ala Met Leu Asp Val Asp
1 5 10 15

<210> SEQ ID NO 107
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 107

Asn His His His Ala Ala Met Leu Asp Val Asp Leu His Pro Ala
1 5 10 15

<210> SEQ ID NO 108
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 108

Ala Ala Met Leu Asp Val Asp Leu His Pro Ala Ser Ala Trp Thr
1 5 10 15

<210> SEQ ID NO 109
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 109

Asp Val Asp Leu His Pro Ala Ser Ala Trp Thr Leu Tyr Ala Val
1 5 10 15

<210> SEQ ID NO 110
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 110

His Pro Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Ile
1 5 10 15

<210> SEQ ID NO 111
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 111

Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Ile Ile Thr Pro Met
1 5 10 15

<210> SEQ ID NO 112
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 112

Tyr Ala Val Ala Thr Thr Ile Ile Thr Pro Met Met Arg His Thr
1 5 10 15

<210> SEQ ID NO 113
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 113

Thr Thr Ile Ile Thr Pro Met Met Arg His Thr Ile Glu Asn Thr
1 5 10 15

<210> SEQ ID NO 114
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 114

Thr Pro Met Met Arg His Thr Ile Glu Asn Thr Thr Ala Asn Ile
1 5 10 15

<210> SEQ ID NO 115
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 115

Arg His Thr Ile Glu Asn Thr Thr Ala Asn Ile Ser Leu Thr Ala
1 5 10 15

<210> SEQ ID NO 116
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 116

Glu Asn Thr Thr Ala Asn Ile Ser Leu Thr Ala Ile Ala Asn Gln
1 5 10 15

<210> SEQ ID NO 117
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 117

Ala Asn Ile Ser Leu Thr Ala Ile Ala Asn Gln Ala Ala Ile Leu
1 5 10 15

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<210> SEQ ID NO 118
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<212> TYPE: PRT
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 118

Gly Trp Pro Ile Ser Lys Met Asp Ile Gly Val Pro Leu Leu Ala
1 5 10 15

<210> SEQ ID NO 119
<211> LENGTH: 15
<212> TYPE: PRT
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<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 119

Ser Lys Met Asp Ile Gly Val Pro Leu Leu Ala Leu Gly Cys Tyr
1 5 10 15

<210> SEQ ID NO 120
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 120

Ile Gly Val Pro Leu Leu Ala Leu Gly Cys Tyr Ser Gln Val Leu
1 5 10 15

<210> SEQ ID NO 121
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 121

Asp Glu Asp Asn Pro Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr
1 5 10 15

<210> SEQ ID NO 122
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 122

Pro Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr Glu Val Lys Pro
1 5 10 15

<210> SEQ ID NO 123
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 123

Trp Ala Tyr His Gly Ser Tyr Glu Val Lys Pro Ser Gly Ser Ala
1 5 10 15

<210> SEQ ID NO 124

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<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 124

Gly Ser Tyr Glu Val Lys Pro Ser Gly Ser Ala Ser Ser Met Val
1 5 10 15

<210> SEQ ID NO 125
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 125

Val Lys Pro Ser Gly Ser Ala Ser Ser Met Val Asn Gly Val Val
1 5 10 15

<210> SEQ ID NO 126
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 126

Gly Ser Ala Ser Ser Met Val Asn Gly Val Val Lys Leu Leu Thr
1 5 10 15

<210> SEQ ID NO 127
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 127

Ser Met Val Asn Gly Val Val Lys Leu Leu Thr Lys Pro Trp Asp
1 5 10 15

<210> SEQ ID NO 128
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 128

Gly Val Val Lys Leu Leu Thr Lys Pro Trp Asp Val Ile Pro Met
1 5 10 15

<210> SEQ ID NO 129
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 129

Leu Leu Thr Lys Pro Trp Asp Val Ile Pro Met Val Thr Gln Ile
1 5 10 15

<210> SEQ ID NO 130
<211> LENGTH: 15

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 130

Pro Trp Asp Val Ile Pro Met Val Thr Gln Ile Ala Met Thr Asp
1 5 10 15

<210> SEQ ID NO 131
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 131

Ile Pro Met Val Thr Gln Ile Ala Met Thr Asp Thr Thr Pro Phe
1 5 10 15

<210> SEQ ID NO 132
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 132

Thr Gln Ile Ala Met Thr Asp Thr Thr Pro Phe Gly Gln Gln Arg
1 5 10 15

<210> SEQ ID NO 133
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 133

Met Thr Asp Thr Thr Pro Phe Gly Gln Gln Arg Val Phe Lys Glu
1 5 10 15

<210> SEQ ID NO 134
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 134

Phe Thr Met Arg Leu Leu Ser Pro Val
1 5

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<212> TYPE: PRT
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<400> SEQUENCE: 135

Val Ala Val Glu Asn His His His Ala Ala Met
1 5 10

<210> SEQ ID NO 136
<211> LENGTH: 9
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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 136

Leu Tyr Ala Val Ala Thr Thr Ile Ile
1 5

<210> SEQ ID NO 137
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 137

Thr Ala Ile Ala Asn Gln Ala Ala Ile
1 5

<210> SEQ ID NO 138
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 138

Ser Ser Met Val Asn Gly Val Val Lys Leu
1 5 10

<210> SEQ ID NO 139
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<222> LOCATION: (19599)..(19606)
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<223> OTHER INFORMATION: pTM plasmid

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cttgtccgag tggcgaggta taccacaatc tccaacgaca atctctcatt tgtcatatca 16680

gataagaagg ttgatactaa ctttatatac caacaaggaa tgcttctagg gttgggtgtt 16740

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cgcaagctag agctgagggc agagctatgt accaacccat tgatatatga taatgcacct 16920

ttaattgaca gagatgcaac aaggctatac acccagagcc ataggaggca ccttgtggaa 16980

tttgttacat ggtccacacc ccaactatat cacattttag ctaagtccac agcactatct 17040

atgattgacc tggtaacaaa atttgagaag gaccatatga atgaaatttc agctctcata 17100

ggggatgacg atatcaatag tttcataact gagtttctgc tcatagagcc aagattattc 17160

actatctact tgggccagtg tgcggccatc aattgggcat ttgatgtaca ttatcataga 17220

ccatcaggga aatatcagat gggtgagctg ttgtcatcgt tcctttctag aatgagcaaa 17280

ggagtgttta aggtgcttgt caatgctcta agccacccaa agatctacaa gaaattctgg 17340

cattgtggta ttatagagcc tatccatggt ccttcacttg atgctcaaaa cttgcacaca 17400

actgtgtgca acatggttta cacatgctat atgacctacc tcgacctgtt gttgaatgaa 17460

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gatgttgcaa aattgctcaa agatatcaac acaagcaagc acaatcttcc catttcaggg 17940

ggcaatctcg ccaattatga aatccatgct ttccgcagaa tcgggttgaa ctcatctgct 18000

tgctacaaag ctgttgagat atcaacatta attaggagat gccttgagcc aggggaggac 18060

ggcttgttct tgggtgaggg atcgggttct atgttgatca cttataaaga gatacttaaa 18120

ctaaacaagt gcttctataa tagtggggtt tccgccaatt ctagatctgg tcaaagggaa 18180

ttagcaccct atccctccga agttggcctt gtcgaacaca gaatgggagt aggtaatatt 18240

gtcaaagtgc tctttaacgg gaggcccgaa gtcacgtggg taggcagtgt agattgcttc 18300

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aatttcatag ttagtaatat ccctacctct agtgtggggt ttatccattc agatatagag 18360

accttgcctg acaaagatac tatagagaag ctagaggaat tggcagccat cttatcgatg 18420

gctctgctcc tgggcaaaat aggatcaata ctggtgatta agcttatgcc tttcagcggg 18480

gattttgttc agggatttat aagttatgta gggtctcatt atagagaagt gaaccttgta 18540

taccctagat acagcaactt catctctact gaatcttatt tggttatgac agatctcaag 18600

gctaaccggc taatgaatcc tgaaaagatt aagcagcaga taattgaatc atctgtgagg 18660

acttcacctg gacttatagg tcacatccta tccattaagc aactaagctg catacaagca 18720

attgtgggag acgcagttag tagaggtgat atcaatccta ctctgaaaaa acttacacct 18780

atagagcagg tgctgatcaa ttgcgggttg gcaattaacg gacctaagct gtgcaaagaa 18840

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tacagggagt tggcaagatt caaagacaac caaagaagtc aacaagggat gttccacgct 18960

taccccgtat tggtaagtag caggcaacga gaacttatat ctaggatcac ccgcaaattc 19020

tgggggcaca ttcttcttta ctccgggaac aaaaagttga taaataagtt tatccagaat 19080

ctcaagtccg gctatctgat actagactta caccagaata tcttcgttaa gaatctatcc 19140

aagtcagaga aacagattat tatgacgggg ggtttgaaac gtgagtgggt ttttaaggta 19200

acagtcaagg agaccaaaga atggtataag ttagtcggat acagtgccct gattaaggac 19260

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ggctgctgcc accgctgagc aataactagc ataacccctt ggggcctcta aacgggtctt 19560

gaggggtttt ttgctgaaag gaggaactat atccggatgc ggccgcgggc cctatggtac 19620

ccagcttttg ttcccttag tgagggttaa ttccgagctt ggcgtaatca tggtcatagc 19680

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tgcgctcggt cgttcggctg cggcgagcgg tatcagctca ctcaaaggcg gtaatacggt 19980

tatccacaga atcaggggat aacgcaggaa agaacatgtg agcaaaaggc cagcaaaagg 20040

ccaggaaccg taaaaaggcc gcgttgctgg cgtttttcca taggctcggc cccctgacg 20100

agcatcacaa aaatcgacgc tcaagtcaga ggtggcgaaa cccgacagga ctataaagat 20160

accaggcgtt ccccctgga agctccctcg tgcgctctcc tgttccgacc ctgccgctta 20220

ccggatacct gtccgccttt ctcccttcgg gaagcgtggc gctttctcaa tgctcacgct 20280

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ccgttcagcc cgaccgctgc gccttatccg gtaactatcg tcttgagtcc aacccggtaa 20400

gacacgactt atcgccactg gcagcagcca ctggtaacag gattagcaga gcgaggtatg 20460

taggcggtgc tacagagttc ttgaagtggt ggcctaacta cggctacact agaaggacag 20520

tatttggtat ctgcgctctg ctgaagccag ttaccttcgg aaaaagagtt ggtagctctt 20580

gatccggcaa acaaaccacc gctggtagcg gtggtttttt tgtttgcaag cagcagatta 20640

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cgcgcagaaa aaaaggatct caagaagatc ctttgatctt ttctacgggg tctgacgctc 20700

agtggaacga aaactcacgt taagggattt tggtcatgag attatcaaaa aggatcttca 20760

cctagatcct tttaaattaa aaatgaagtt ttaaatcaat ctaaagtata tatgagtaaa 20820

cttggtctga cagttaccaa tgcttaatca gtgaggcacc tatctcagcg atctgtctat 20880

ttcgttcatc catagttgcc tgactgcccg tcgtgtagat aactacgata cgggagggct 20940

taccatctgg ccccagtgct gcaatgatac cgcgagaccc acgctcaccg gctccagatt 21000

tatcagcaat aaaccagcca gccggaaggg ccgagcgcag aagtggtcct gcaactttat 21060

ccgcctccat ccagtctatt aattgttgcc gggaagctag agtaagtagt tcgccagtta 21120

atagtttgcg caacgttgtt gccattgcta caggcatcgt ggtgtcacgc tcgtcgtttg 21180

gtatggcttc attcagctcc ggttcccaac gatcaaggcg agttacatga tcccccatgt 21240

tgtgaaaaaa agcggttagc tccttcggtc ctccgatcgt tgtcagaagt aagttggccg 21300

cagtgttatc actcatgctt atggcagcac tgcataattc tcttactgtc atgccatccg 21360

taagatgctt ttctgtgact ggtgagtact caaccaagtc attctgagaa tagtgtatgc 21420

ggcgaccgag ttgctcttgc ccggcgtcaa tacgggataa taccgcgcca catagcagaa 21480

ctttaaaagt gctcatcatt ggaaaacgtt cttcggggcg aaaactctca aggatcttac 21540

cgctgttgag atccagttcg atgtaaccca ctcgtgcacc caactgatct tcagcatctt 21600

ttactttcac cagcgtttct gggtgagcaa aaacaggaag gcaaaatgcc gcaaaaaagg 21660

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aacaaatagg ggttccgcgc acatttcccc gaaaagtgcc acctgaaatt gtaaacgtta 21840

atattttgtt aaaattcgcg ttaaattttt gttaaatcag ctcatttttt aaccaatagg 21900

ccgaaatcgg caaaatccct tataaatcaa aagaatagac cgagataggg ttgagtgttg 21960

ttccagtttg gaacaagagt ccactattaa agaacgtgga ctccaacgtc aaagggcgaa 22020

aaaccgtcta tcagggcgat ggcccactac gtgaaccatc accctaatca agtttttggg 22080

ggtcgaggtg ccgtaaagca ctaaatcgga accctaaagg gagcccccga tttagagctt 22140

gacggggaaa gccggcgaac gtggcgagaa aggaagggaa gaaagcgaaa ggagcgggcg 22200

ctagggcgct ggcaagtgta gcggtcacgc tgcgcgtaac caccacaccc gccgcgctta 22260

atgcgccgct acagggcgcg tcccattcgc cattcaggct gcgcaactgt tgggaagggc 22320

gatcggtgcg ggcctcttcg ctattacgcc agccaccgcg gtg 22363

<210> SEQ ID NO 144
<211> LENGTH: 1554
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Nucleotide sequence of the polynucleotide encoding DENV tetra EDIII-ectoM

<400> SEQUENCE: 144

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atcaaaggta tgagctatac gatgtgcagc ggcaagttca agatcgagaa ggaaatggct 120

gaaacccagc acggtacaac tgtggtcaaa gtcaaatatg agggggctgg cgctccctgt 180

aaagtaccca ttgagattag ggacgtcaat aaagagaagg tggtaggtcg catcatctcc 240

agtacacctt tggccgagaa cacgaactcc gtcacaaaca tagagttgga acccccgttc 300

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```
ggagactcat acattgtgat cggggtgggc aactctgcac tcacactgca ttggttcaag    360

aagggaagca gtatcggccg cagggataag agagacaaac tgaaattgaa aggtatgtcc    420

tatgccatgt gcacgaatac tttcgttctc aagaaagaag tatctgagac tcagcacgga    480

accatcctga tcaaagtcga gtacaaagga gaagacgtgc cctgtaagat cccattcagt    540

accgaggatg gacagggcaa ggcccataac ggcaggctga taaccgccaa ccctgtggtt    600

acaaagaagg aagagccagt caatatcgaa gctgagccac cgttcgggga gagcaacata    660

gtaattggca taggggataa tgctttgaag atcaactggt acaagaaagg aagctccatt    720

ggccgaagag ataagcgcga caaactccag ctgaaaggaa tgagctactc catgtgtact    780

gggaagttca agattgtcaa ggaaatcgcc gaaactcagc atggcactat tgtgatccgc    840

gtgcagtatg aaggcgatgg tagcccctgc aagataccat ttgaaatcac cgatttggag    900

aaacggcacg tcctgggtcg gctcattacc gtgaacccaa tcgtgaccga gaaggacagt    960

ccagttaata tcgaggccga gcctcctttc ggcgacagtt acatcattgt aggggtggaa   1020

ccagggcaac tgaagctgaa ctggttcaag aaaggcagca gtataggacg gcgggataaa   1080

cgggacaaac tcacactgaa aggcatgtca tacgttatgt gcaccggctc attcaaactg   1140

gagaaggaag ttgcagagac acagcatggg accgtgctcg tgcaggtcaa atacgagggc   1200

accgacgctc cttgcaagat tccgttcagt acacaggacg agaaaggcgt gactcagaac   1260

ggcagattga ttacagcgaa ccctatcgtg actgacaagg agaagccagt taacatcgag   1320

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ctcagctggt tcaagaaggg cagctcaatc ggtcggagag acaagcggtc tgtcgccctc   1440

gcaccgcacg tgggcctggg tctggaaacg aggaccgaga cgtggatgag ttccgaaggc   1500

gcatggaagc aaatccagaa agtggagacg tgggccctca ggcatccgta atga         1554
```

<210> SEQ ID NO 145
<211> LENGTH: 516
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of DENV tetra EDIII-ectoM

<400> SEQUENCE: 145

```
Met Gly Ile Ile Phe Ile Leu Leu Met Leu Val Thr Pro Ser Met Ala
1               5                   10                  15

Glu Lys Leu Arg Ile Lys Gly Met Ser Tyr Thr Met Cys Ser Gly Lys
            20                  25                  30

Phe Lys Ile Glu Lys Glu Met Ala Glu Thr Gln His Gly Thr Thr Val
        35                  40                  45

Val Lys Val Lys Tyr Glu Gly Ala Gly Ala Pro Cys Lys Val Pro Ile
    50                  55                  60

Glu Ile Arg Asp Val Asn Lys Glu Lys Val Val Gly Arg Ile Ile Ser
65                  70                  75                  80

Ser Thr Pro Leu Ala Glu Asn Thr Asn Ser Val Thr Asn Ile Glu Leu
                85                  90                  95

Glu Pro Pro Phe Gly Asp Ser Tyr Ile Val Ile Gly Val Gly Asn Ser
            100                 105                 110

Ala Leu Thr Leu His Trp Phe Lys Lys Gly Ser Ser Ile Gly Arg Arg
        115                 120                 125

Asp Lys Arg Asp Lys Leu Lys Leu Lys Gly Met Ser Tyr Ala Met Cys
    130                 135                 140
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Thr Asn Thr Phe Val Leu Lys Lys Glu Val Ser Glu Thr Gln His Gly
145                 150                 155                 160

Thr Ile Leu Ile Lys Val Glu Tyr Lys Gly Glu Asp Val Pro Cys Lys
                165                 170                 175

Ile Pro Phe Ser Thr Glu Asp Gly Gln Gly Lys Ala His Asn Gly Arg
            180                 185                 190

Leu Ile Thr Ala Asn Pro Val Val Thr Lys Lys Glu Glu Pro Val Asn
        195                 200                 205

Ile Glu Ala Glu Pro Pro Phe Gly Glu Ser Asn Ile Val Ile Gly Ile
    210                 215                 220

Gly Asp Asn Ala Leu Lys Ile Asn Trp Tyr Lys Lys Gly Ser Ser Ile
225                 230                 235                 240

Gly Arg Arg Asp Lys Arg Asp Lys Leu Gln Leu Lys Gly Met Ser Tyr
                245                 250                 255

Ser Met Cys Thr Gly Lys Phe Lys Ile Val Lys Glu Ile Ala Glu Thr
            260                 265                 270

Gln His Gly Thr Ile Val Ile Arg Val Gln Tyr Glu Gly Asp Gly Ser
        275                 280                 285

Pro Cys Lys Ile Pro Phe Glu Ile Thr Asp Leu Glu Lys Arg His Val
    290                 295                 300

Leu Gly Arg Leu Ile Thr Val Asn Pro Ile Val Thr Glu Lys Asp Ser
305                 310                 315                 320

Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Asp Ser Tyr Ile Ile
                325                 330                 335

Val Gly Val Glu Pro Gly Gln Leu Lys Leu Asn Trp Phe Lys Lys Gly
            340                 345                 350

Ser Ser Ile Gly Arg Arg Asp Lys Arg Asp Lys Leu Thr Leu Lys Gly
        355                 360                 365

Met Ser Tyr Val Met Cys Thr Gly Ser Phe Lys Leu Glu Lys Glu Val
    370                 375                 380

Ala Glu Thr Gln His Gly Thr Val Leu Val Gln Val Lys Tyr Glu Gly
385                 390                 395                 400

Thr Asp Ala Pro Cys Lys Ile Pro Phe Ser Thr Gln Asp Glu Lys Gly
                405                 410                 415

Val Thr Gln Asn Gly Arg Leu Ile Thr Ala Asn Pro Ile Val Thr Asp
            420                 425                 430

Lys Glu Lys Pro Val Asn Ile Glu Thr Glu Pro Pro Phe Gly Glu Ser
        435                 440                 445

Tyr Ile Ile Val Gly Ala Gly Glu Lys Ala Leu Lys Leu Ser Trp Phe
    450                 455                 460

Lys Lys Gly Ser Ser Ile Gly Arg Arg Asp Lys Arg Ser Val Ala Leu
465                 470                 475                 480

Ala Pro His Val Gly Leu Gly Leu Glu Thr Arg Thr Glu Thr Trp Met
                485                 490                 495

Ser Ser Glu Gly Ala Trp Lys Gln Ile Gln Lys Val Glu Thr Trp Ala
            500                 505                 510

Leu Arg His Pro
        515
```

<210> SEQ ID NO 146
<211> LENGTH: 537
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the chimeric polyepitope

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of DENV2

<400> SEQUENCE: 146

```
Lys Ser Ile Glu Asp Asn Pro Glu Ile Glu Asp Asp Ile Phe Arg Lys
1               5                  10                  15

Lys Arg Leu Thr Ile Met Asp Leu His Pro Gly Ala Gly Lys Thr Lys
            20                  25                  30

Arg Tyr Leu Pro Ala Ile Val Arg Glu Ala Ile Lys Arg Gly Leu Arg
        35                  40                  45

Thr Leu Ile Leu Ala Pro Thr Arg Val Val Ala Ala Glu Met Glu Glu
    50                  55                  60

Ala Leu Arg Gly Leu Pro Ile Arg Tyr Gln Thr Pro Ala Ile Arg Ala
65                  70                  75                  80

Glu His Thr Gly Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Phe
                85                  90                  95

Thr Met Arg Leu Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Leu Ile
            100                 105                 110

Ile Met Asp Glu Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg
        115                 120                 125

Gly Tyr Ile Ser Thr Arg Val Glu Met Gly Glu Ala Ala Gly Ile Phe
    130                 135                 140

Met Thr Ala Thr Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser Asn
145                 150                 155                 160

Ala Pro Ile Met Asp Glu Glu Arg Glu Ile Pro Glu Arg Ser Trp Asn
                165                 170                 175

Ser Gly His Glu Trp Val Thr Asp Glu Asp Cys Ala His Trp Lys Glu
            180                 185                 190

Ala Lys Met Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro
        195                 200                 205

Ser Met Phe Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu
    210                 215                 220

Tyr Arg Leu Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg
225                 230                 235                 240

Arg Gly Asp Leu Pro Val Trp Leu Ala Tyr Lys Val Ala Ala Glu Gly
                245                 250                 255

Ile Asn Tyr Ala Asp Arg Arg Trp Cys Phe Asp Gly Ile Lys Asn Asn
            260                 265                 270

Gln Ile Leu Glu Glu Asn Val Glu Val Glu Ile Trp Thr Lys Glu Gly
        275                 280                 285

Glu Arg Lys Lys Leu Lys Pro Arg Trp Leu Asp Ala Arg Ile Tyr Ser
    290                 295                 300

Asp Pro Leu Ala Leu Lys Glu Phe Lys Glu Phe Ala Ala Gly Ile Thr
305                 310                 315                 320

Thr Gln Glu Ser Glu Ser Asn Ile Leu Asp Ile Asp Leu Arg Pro Ala
                325                 330                 335

Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Phe Val Thr Pro Met
            340                 345                 350

Leu Arg His Ser Ile Glu Asn Ser Ser Val Asn Val Ser Leu Thr Ala
        355                 360                 365

Ile Ala Asn Gln Ala Thr Val Leu Met Gly Leu Gly Lys Gly Trp Pro
    370                 375                 380

Leu Ser Lys Met Asp Ile Gly Val Pro Leu Leu Ala Ile Gly Cys Tyr
385                 390                 395                 400
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Ser Gln Val Leu Asp Ile Ile Gly Lys Arg Ile Glu Lys Ile Lys Gln
                405                 410                 415

Glu His Glu Thr Ser Trp His Tyr Asp Gln Asp His Pro Tyr Lys Thr
            420                 425                 430

Trp Ala Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly Ser Ala Ser
        435                 440                 445

Ser Met Val Asn Gly Val Val Arg Leu Leu Thr Lys Pro Trp Asp Val
    450                 455                 460

Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Thr Pro Phe Gly
465                 470                 475                 480

Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr Gln Glu Pro
                485                 490                 495

Lys Glu Gly Thr Lys Lys Leu Met Lys Ile Thr Ala Glu Trp Leu Trp
            500                 505                 510

Lys Glu Leu Gly Lys Lys Lys Thr Pro Arg Met Cys Thr Arg Glu Glu
        515                 520                 525

Phe Thr Arg Lys Val Arg Ser Asn Ala
    530                 535


<210> SEQ ID NO 147
<211> LENGTH: 538
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the chimeric polyepitope
      of DENV3

<400> SEQUENCE: 147

Ala Glu Pro Asp Gly Pro Thr Pro Glu Leu Glu Glu Met Phe Lys
1               5                   10                  15

Lys Arg Asn Leu Thr Ile Met Asp Leu His Pro Gly Ser Gly Lys Thr
            20                  25                  30

Arg Lys Tyr Leu Pro Ala Ile Val Arg Glu Ala Ile Lys Arg Arg Leu
        35                  40                  45

Arg Thr Leu Ile Leu Ala Pro Thr Arg Val Val Ala Ala Glu Met Glu
    50                  55                  60

Glu Ala Leu Lys Gly Leu Pro Ile Arg Tyr Gln Thr Thr Ala Thr Lys
65                  70                  75                  80

Ser Glu His Thr Gly Arg Glu Ile Val Asp Leu Met Cys His Ala Thr
                85                  90                  95

Phe Thr Met Arg Leu Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Leu
            100                 105                 110

Ile Ile Met Asp Glu Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala
        115                 120                 125

Arg Gly Tyr Ile Ser Thr Arg Val Gly Met Gly Glu Ala Ala Ala Ile
    130                 135                 140

Phe Met Thr Ala Thr Pro Pro Gly Thr Ala Asp Ala Phe Pro Gln Ser
145                 150                 155                 160

Asn Ala Pro Ile Gln Asp Glu Glu Arg Asp Ile Pro Glu Arg Ser Trp
                165                 170                 175

Asn Ser Gly Asn Glu Trp Ile Thr Asp Glu Asp His Ala His Trp Thr
            180                 185                 190

Glu Ala Lys Met Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile
        195                 200                 205

Pro Ala Leu Phe Glu Pro Glu Arg Glu Lys Ser Ala Ala Ile Asp Gly
    210                 215                 220
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Glu Tyr Arg Leu Lys Gly Glu Ser Arg Lys Thr Phe Val Glu Leu Met
225                 230                 235                 240

Arg Arg Gly Asp Leu Pro Val Trp Leu Ala His Lys Val Ala Ser Glu
                245                 250                 255

Gly Ile Lys Tyr Thr Asp Arg Lys Trp Cys Phe Asp Gly Gln Arg Asn
            260                 265                 270

Asn Gln Ile Leu Glu Glu Asn Met Asp Val Glu Ile Trp Thr Lys Glu
        275                 280                 285

Gly Glu Lys Lys Lys Leu Arg Pro Arg Trp Leu Asp Ala Arg Thr Tyr
    290                 295                 300

Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys Asp Phe Ala Ala Gly Glu
305                 310                 315                 320

Pro Gly Val Val Ser Pro Thr Ser Tyr Leu Asp Val Asp Leu His Pro
                325                 330                 335

Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Val Ile Thr Pro
            340                 345                 350

Met Leu Arg His Thr Ile Glu Asn Ser Thr Ala Asn Val Ser Leu Ala
        355                 360                 365

Ala Ile Ala Asn Gln Ala Val Val Leu Met Gly Leu Asp Lys Gly Trp
    370                 375                 380

Pro Ile Ser Lys Met Asp Leu Gly Val Pro Leu Leu Ala Leu Gly Cys
385                 390                 395                 400

Tyr Ser Gln Val Met Asp Val Ile Gly Glu Arg Ile Lys Arg Ile Lys
                405                 410                 415

Glu Glu His Asn Ser Thr Trp His Tyr Asp Asp Glu Asn Pro Tyr Lys
            420                 425                 430

Thr Trp Ala Tyr His Gly Ser Tyr Glu Val Lys Ala Thr Gly Ser Ala
        435                 440                 445

Ser Ser Met Ile Asn Gly Val Val Lys Leu Leu Thr Lys Pro Trp Asp
    450                 455                 460

Val Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Thr Pro Phe
465                 470                 475                 480

Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr Pro Arg
                485                 490                 495

Ser Met Pro Gly Thr Arg Arg Val Met Gly Ile Thr Ala Glu Trp Leu
            500                 505                 510

Trp Arg Thr Leu Gly Arg Asn Lys Lys Pro Arg Leu Cys Thr Arg Glu
        515                 520                 525

Glu Phe Thr Lys Lys Val Arg Thr Asn Ala
    530                 535


<210> SEQ ID NO 148
<211> LENGTH: 534
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Amino acid sequence of the chimeric polyepitope
      of DENV4

<400> SEQUENCE: 148

Arg Ile Gly Glu Pro Asp Tyr Glu Val Asp Glu Asp Ile Phe Arg Lys
1               5                   10                  15

Lys Arg Leu Thr Ile Met Asp Leu His Pro Gly Ala Gly Lys Thr Lys
            20                  25                  30

Arg Ile Leu Pro Ser Ile Val Arg Glu Ala Leu Lys Arg Arg Leu Arg
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        35                  40                  45

Thr Leu Ile Leu Ala Pro Thr Arg Val Val Ala Ala Glu Met Glu Glu
    50                  55                  60

Ala Leu Arg Gly Leu Pro Ile Arg Tyr Gln Thr Pro Ala Val Lys Ser
65                  70                  75                  80

Glu His Thr Gly Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Phe
                85                  90                  95

Thr Thr Arg Leu Leu Ser Ser Thr Arg Val Pro Asn Tyr Asn Leu Ile
            100                 105                 110

Val Met Asp Glu Ala His Phe Thr Asp Pro Ser Ser Val Ala Ala Arg
        115                 120                 125

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The invention claimed is:

1. A chimeric polyepitope polypeptide having an amino acid sequence of less than 600 amino acid residues comprising polypeptide fragments (a), (b), (c), and (d) directly or indirectly fused in this order:

(a) a first fragment of the non-structural (NS) NS3 protein of dengue virus (DENV) serotype 1 (DENV1) comprising an amino acid sequence as defined in SEQ ID NO: 6,

(b) a second fragment of the NS3 protein of DENV1 comprising an amino acid sequence as defined in SEQ ID NO: 9,

(c) a fragment of the NS4b protein of DENV1 comprising an amino acid sequence as defined in SEQ ID NO: 12, and

(d) a fragment of the NS5 protein of DENV1 comprising an amino acid sequence as defined in SEQ ID NO: 15;

or a variant of the chimeric polyepitope polypeptide having an amino acid sequence more than 80% identical to the amino acid sequence of the chimeric polyepitope polypeptide over its whole length;

wherein the chimeric polyepitope polypeptide elicits a human leukocyte antigen (HLA)-restricted $CD8^+$ and/or $CD4^+$ T cell response against DENV1, DENV2, DENV3 and DENV4.

2. The chimeric polyepitope polypeptide according to claim **1**, which comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NOs: 146, SEQ ID NO: 147 and SEQ ID NO: 148.

3. Recombinant measles virus (MV) particles, which are rescued from a helper cell line expressing the T7 RNA polymerase and the N, P and L proteins of MV, and which further expresses a polynucleotide encoding the chimeric polyepitope polypeptide of claim **1**.

4. An immunogenic composition comprising (a) DENV antigens composed of the fusion of the EDIII polypeptides of the four DENV serotypes, fused to ectoM of DENV1, wherein the DENV antigens have the sequence of SEQ ID NO: 145; and (b) the chimeric polyepitope polypeptide according to claim **1**.

5. An immunogenic composition comprising recombinant MV particles according to claim **3**.

6. The immunogenic composition according to claim **4**, wherein said composition is formulated for an administration through parenteral route such as subcutaneous (s.c.), intradermal (i.d.), intramuscular (i.m.), intraperitoneal (i.p.) or intravenous (i.v.) injection.

7. The immunogenic composition according to claim **4**, wherein said composition is formulated for administration in one or multiple administration dose(s) in a prime-boost administration regime.

8. The chimeric polyepitope polypeptide according to claim **1**, wherein the chimeric polyepitope polypeptide consists of polypeptide fragments (a), (b), (c), and (d).

9. A method to immunize a human subject against a dengue virus infection comprising administering a pharmaceutically effective quantity of recombinant MV particles according to claim **3**, wherein said particles are in admixture with a pharmaceutically acceptable vehicle and/or an adjuvant.

10. A method to treat a dengue virus infection in a human subject comprising administering a pharmaceutically effective quantity of recombinant MV particles according to claim **3**, wherein said particles are in admixture with a pharmaceutically acceptable vehicle and/or an adjuvant.

* * * * *